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Recommendations for collaborative paediatric research including biobanking in Europe - A Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) Initiative

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Keywords:	Juvenile Idiopathic Arthritis, Gene Polymorphism, Treatment, Multidisciplinary team-care

Dear Reviewers, dear members of the Editorial Board

Thank you for the kind and thorough review of our manuscript. We hope we have addressed all questions sufficiently and have made all suggested changes in the re-submission.

Editor requests

1) You may consider to cite some of the previously published papers from the SHARE initiative - to put the current paper into a wider context.

Response: We have added the following publication in addition to the "Time to SHARE" reference (REF 4):

- European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Groot N, Graeff N, Avcin T, Bader-Meunier B, Brogan P, Dolezalova P, Feldman B, Kone-Paut I, Lahdenne P, Marks SD, McCann L, Ozen S, Pilkington C, Ravelli A, Royen-Kerkhof AV, Uziel Y, Vastert B, Wulffraat N, Kamphuis S, Beresford MW. Ann Rheum Dis. 2017 Jun 19. pii: annrheumdis-2016-210960. doi: 10.1136/annrheumdis-2016-210960. [Epub ahead of print]
- Recommendations for the management of autoinflammatory diseases.ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, Cantarini L, Galeotti C, Grateau G, Hentgen V, Hofer M, Kallinich T, Kone-Paut I, Lachmann HJ, Ozdogan H, Ozen S, Russo R, Simon A, Uziel Y, Wouters C, Feldman BM, Vastert SJ, Wulffraat NM, Benseler SM, Frenkel J, Gattorno M, Kuemmerle-Deschner JB.Ann Rheum Dis. 2015 Sep;74(9):1636-44.
- Consensus-based recommendations for the management of juvenile dermatomyositis. Enders FB, Bader-Meunier B, Baildam E, Constantin T, Dolezalova P, Feldman BM, Lahdenne P, Magnusson B, Nistala K, Ozen S, Pilkington C, Ravelli A, Russo R, Uziel Y, van Brussel M, van der Net J, Vastert S, Wedderburn LR, Wulffraat N, McCann LJ, van Royen-Kerkhof A. Ann Rheum Dis. 2017 Feb;76(2):329-340. doi: 10.1136/annrheumdis-2016-209247. Epub 2016 Aug 11. Review.
- European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative.Groot N, de Graeff N, Avcin T, Bader-Meunier B, Dolezalova P, Feldman B, Kenet G, Koné-Paut I, Lahdenne P, Marks SD, McCann L, Pilkington CA, Ravelli A, van Royen-Kerkhof A, Uziel Y, Vastert SJ, Wulffraat NM, Ozen S, Brogan P, Kamphuis S, Beresford MW. Ann Rheum Dis. 2017 May 4. pii: annrheumdis-2016-211001. doi: 10.1136/annrheumdis-2016-211001. [Epub ahead of print]

(page 5)

2) Supplemental Table 2 should be supplementary Table S1.

Response: We made the change as suggested (see online supplementary material).

3) I assume you plan to include what you now call appendix into the online supplement. If you need to add any material, please be aware that text, figures and tables can be published as online supplementary material. Online figures and tables should have separate numbers – Figure S1, S2 etc, Table S1, S2 etc. You may refer to the supplementary material in the main text as follows: (see online supplementary text / online supplementary Table S1, S2 etc /online supplementary Figure S1, S2 etc – as appropriate).
Response: Yes, thanks for the kind suggestion. We modified the titles accordingly (see online supplementary material).

FORMATTING AMENDMENTS

1) Tables meant for print publication should not exceed 2 pages. If they are, reduce the size or upload them as Supplementary file, to be published as Online only.
Response: We have modified the format of Table 1 as requested in two ways, a landscape format with 8pt fond and a removal of all explanatory text (option 2). These two options are submitted together as a separate document. However, we strongly believe Table 1 should be kept in the document in the original version and not be moved to the online supplementary material, since it is of key interest for the readers.

2) Please make sure the following statements are included in the main document file, which should match the details given in the submission pages: Competing interests, Acknowledgements, Contributorship, Funding info
Response: We modified the main document as requested and added the following statements:
Competing interests: None declared.
Acknowledgements: None.
Contributorship: All authors have contributed to the study design, data gathering, analysis and preparation of the submitted manuscript.
Funding info: SHARE was funded by the European Agency for Health and Consumers (EAHC), No. 2011 1202**.**
(see page 3)

Reviewer 1
1) Comment to the author: The authors have proposed a SHARE model for conducting research in pediatric Rheumatology. Overall the manuscript details the procedure followed in arriving at a consensus.
Response: Thank you very much for the important comment. The manuscript is the reflection of the process resulting in the evidence-based and consensus-supported proposed recommendations for collaborative paediatric research. We are hoping these are capturing the complexity of the process and will be helpful in advancing collaborative paediatric research including biobanking.

2) The reason for changing from the UNESCO International Declaration on Human Genetic Data the right of an individual to decide whether or not to be informed of the results of genetic tests are not very clear. I am not sure if it is a barrier to participation. If mutation for Huntigton's chorea is found in GWAS study would it be told to family.
Response: The reviewer raises a critically important challenge in pediatric research. While the "right to not know" is clearly defined in the UNESCO International Declaration on Human Genetic Data and fully applicable for adults, the situation for children is more complicated. In paediatric research, the decision maker commonly is the parent or legal guardian not the participating child. Information generated in research studies that have to result in medical attention ("clinically relevant results") have to be shared in order to facilitate treatment for the child (see Hens 2011). This is reflected in the proposed recommendations. Refusal to be informed about clinically relevant results therefore has to represent an exclusion criterion for participation in pediatric research studies.
We modified the results as follows
"Refusal to be informed about clinically relevant findings therefore represents a barrier for the participation of minors in research[25]; parents cannot make the choice for their children not be informed about clinically relevant results." (page 12).

3) Appendix can be moved to supplementary data
Response: we moved the appendix to the online supplementary material (see Table S2)

Reviewer: 2

1) The language is mostly clear and concise. Some mistakes like “focussing” (twice in page 7), and “a” instead of “an” etc several places should be corrected
Response: We removed the repeated mistakes of “focussing” on page 6. We also corrected the wrong "a" used in the text throughout the document.

2) The abstract is appropriate
Response: Thank you.

3) METHODS are sound, adequate for the task, and precisely described
Response: Thank you.

4) METHODS and FIGURE 1
a) It is unclear to me if the inclusion of normative documents as level 1 in the modified hierarchy of evidence pyramid, while systematic reviews and RCT are level II a and II b, is a construction of the authors? I was not able to find this approach at the CEBM website in the references. Please clarify
Response: The reviewer raises a critically important question, which we have struggled with and proactively addressed when conducting the research. Similar to the reviewer, we were unable to find a publication defining the assigned evidence level of normative documents. Rather than constructing our own evidence ranking, we connected with the Cochrane Foundation directly and were instructed to rank normative documents as level

1 evidence. We referred to this as "modification of the evidence ranking system supported by the Cochrane group" (page 6).

b) International normative documents have been used in this manuscript as level 1 in the modified hierarchy of evidence pyramid, while systematic reviews and RCT are level II a and II b. All recommendations for collaborative paediatric research must of course be in line with these normative documents. However, regulations, guidelines, and legislation may change with rapidly evolving registries, biobanking, genetic, and other research possibilities, even though the Human rights and Helsinki declarations are constant. I would suggest to have the international normative documents as a background triangle outside all the levels of the pyramid, rather than at the top of the pyramid, and could still be designated Grade A of Recommendation. The other approach is the choice of the authors, and the whole manuscript cannot be changed after the nominative group process has taken place.
Response: Thanks you for the great suggestion. We modified Figure 1 as requested.

I still challenge the authors to discuss this choice of comparing normative documents with scientific papers in the DISCUSSION section.
Response: Thank you for the kind encouragement. We modified the Discussion as requested.
"This framework is the first of its kind. It was built upon a comprehensive review of published evidence, guidance of European leaders in ethics and law, and practical experience of leading paediatric researchers, and expert clinicians. Normative documents including ratified European laws and international declarations were reviewed and served as high-level evidence, an approach common to the area of ethics research, yet unfamiliar to medical researcher. Most importantly, the process has integrated the perspective of families living with childhood rare diseases." (page 13)

5) METHODS Page 9, line 46, Please state the evidence level after “cross-sectional studies”.
Response: We added the level of evidence as requested and modified the manuscript as follows: "Among the 85 retained publications three publications were systematic reviews, defined as evidence level II a (none were II b), 15 were non-systematic reviews (evidence level III), 24 cross-sectional studies (level IV b), 16 narrative reviews, and 27 expert opinions (evidence level V b)." (page 9)

6) DISCUSSION section. The authors state that the key limitation of the study is the lack of generalizability beyond Europe. Please discuss how this problem could be solved (i.e the current work as a model for other regions, inviting other regions and especially less privileged countries to participate in Paediatric Rheumatology collaborative research initiatives across borders, etc)

Response: Thanks for encouraging to further discussing this important aspect. We have expanded on the limitation of generalizability as requested and modified the discussion as follows:

"There are several limitations to the study and its results. The key limitation is the generalizability beyond Europe. Published literature and normative documents applicable to the European context only informed the recommendation development. The transferability into another cultural context such as North or South America has to be explored. When aiming so, the literature search and evidence synthesis would have to include publications and most importantly normative documents beyond Europe. In addition, the expert team had a content and method focus on childhood rheumatic diseases. In order to increase the generalizability care researchers, patients and families with a spectrum of other conditions including common and rare, acute and chronic illnesses would need to be part of the process. The transferability to other childhood diseases could then be tested; recommendations may require additional specifications when applied to a different disease context. However, it appears that principles captured in the proposed set of recommendations are widely generalizable across childhood diseases." (page 14)

Title

Recommendations for collaborative paediatric research including biobanking in Europe – A Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) Initiative

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Word count: 2975

Abstract

Objectives: Innovative research in childhood rheumatic diseases mandates international collaborations. However, researchers struggle with significant regulatory heterogeneity; an enabling EU-wide framework is missing. The aims of the study were to systematically review the evidence for best practice and to establish recommendations for collaborative research.

Methods: The Paediatric Rheumatology European SHARE project enabled a scoping review and expert discussion, which then informed the systematic literature review. Published evidence was synthesized; recommendations were drafted. An iterative review process and consultations with Ethics Committees and European experts for ethical and legal aspects of paediatric research refined the recommendations. SHARE experts and patient representatives vetted the proposed recommendations at a consensus meeting using Nominal Group Technique. Agreement of 80% was mandatory for inclusion.

Results: The systematic literature review returned 1319 records. A total of 223 full-text publications plus 22 international normative documents were reviewed; 85 publications and 16 normative documents were included. A total of 21 recommendations were established including general principles (1-3), ethics (4-7), paediatric principles (8 and 9), consent to paediatric research (10 -14), paediatric data- and biobanks (15 and 16), sharing of data and samples (17 - 19), and commercialization and third parties (20 and 21). The refined recommendations resulted in an agreement of >80% for all recommendations.

Conclusions: The SHARE initiative established the first recommendations for Paediatric Rheumatology collaborative research across borders in Europe. These provide strong support for an urgently needed European framework and evidence-based guidance for its implementation. Such changes will promote research in children with rheumatic diseases.

Introduction

Paediatric rheumatic diseases are rare and often devastating; advancing knowledge and improving care and outcomes of affected children mandates research collaborations across national borders [1-3]. Across Europe, several national innovative research teams have made substantial contributions to developing clinical tools, biomarkers, and imaging strategies for children with rheumatic diseases. Their evaluation and implementation mandates international patient cohorts and research partnerships given that some paediatric rheumatic diseases have incidences as low as one per million.

The European community strongly encourages collaborative international research and funded the “Single Hub and Access point for paediatric Rheumatology in Europe (SHARE)" initiative, which aims to optimize care and research for children with rheumatic diseases across Europe[4-8]. A key task was the identification of barriers between nations for collaborative Paediatric Rheumatology research. Currently, researchers funded to conduct important studies struggle with the substantial heterogeneity within and across European countries in all areas of rare diseases research. These include ethics approval process, consent and assent, formal frameworks for data and sample collection and sharing, and aspects of third party data and sample access. Currently there is no EU-wide framework facilitating the conduct of collaborative rare diseases research[9].

Therefore the aims of the study were to synthesize the evidence for best practice in paediatric rheumatic diseases research and to develop recommendations to enable research collaborations including data- and biobanking across Europe.

Methods

Scoping review and expert consultation

A scoping review on collaborative paediatric research was conducted identifying key themes. In addition, major stakeholders including ethics committee members, European Paediatric Rheumatology researchers, and patients with rare diseases were asked to provide input regarding their perspectives on research and its barriers and challenges using structured interviews by surveys, phone, and in-person. The group identified key themes and constructed an evaluative framework including a modification of the evidence ranking system supported by the Cochrane group (Figure 1).

Systematic review

Search strategy and selection criteria

A systematic literature review anchored in the identified key themes was performed and reported according to the standards of the "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA)" guidelines[10,11]. This systematic search of the literature aimed to identify studies of all aspects of paediatric research in Europe. These were specified in MESH terms and subheadings including data collection, ethics, biological specimen banks, confidentiality, informed consent by minors, specimen handling, jurisprudence, quality improvement, legislation, classification, methods, organization, administration, standards, and instrumentation. The search was performed in the electronic databases PubMed and Web of Science on 14th May 2014. The search was limited to articles published in English and children and adolescents (ages 0-18 years); the search period was set between January 1989 and April 2014, guided by the publication date of the United Nation's Convention on the Rights of the Child[12]. In addition to the electronic literature search, a manual review of the references of all relevant publications and international and European normative documents was conducted. Articles were excluded, if the content was not related to children and adolescents, it did not apply to the European context, or to any aspect of collaborative paediatric research.

Data extraction and validity assessment

The remaining full-text articles were reviewed by a panel of experts, graded by two independent researchers, and reconciled by a third using predefined scoring instruments for the different study and publication types as appropriate[13,14]. The following variables were abstracted: reference, year of publication, authors, country of focus, and contribution to the themes. Levels of evidence and strength of recommendations were determined using an adjusted framework for grading scientific evidence in order to account for normative documents including declarations, regulations, guidelines, and legislative documents[15].

Development and refinement of recommendations

Grouped by distinct themes, the evidence was synthesized; additional domains were developed including public opinion on paediatric research, guidelines, and jurisdiction. Recommendations were drafted. In-depth discussion, iterative reviews, and adjustments of the recommendations were completed with ethics committee staff members and international content experts in paediatric ethics (KH) and legislation (DS). The draft version of the recommendations was sent to all SHARE experts in an online survey format for review and revision. All suggestions were integrated and additional recommendations were drafted; the revised documents were re-distributed to the experts for review and evaluation of agreement.

Consensus meeting

The proposed and reviewed recommendations were presented to the SHARE expert committee and patient representatives during a face-to-face consensus meeting in Rome, Italy, and discussed in-depth using Nominal Group Technique[16]. Recommendations were accepted by reaching agreement above 80%.

Results

Scoping review and expert consultation

The key themes of collaborative paediatric research and biobanking in Paediatric Rheumatology were identified. These included ethics, legislation, consent, scope of consent, confidentiality, anonymisation, sample and data collection, handling, and storage. These were translated into search terms to inform the evidence synthesis.

Systematic literature review

The initial search returned 7347 records, of which 6503 had to be excluded. Ultimately, 1319 publications including 844 from PubMed and 475 papers from the Web of Science Core Collection were identified. After removing 31 duplicates, a total of 1288 records were manually reviewed for title and abstract excluding 1065. Full-text assessment of 223 papers resulted in exclusion of 161. A total of 62 publications plus an additional 23 identified by targeted hand-search from references resulted in 85 papers to be included (see Table S1). A full-text review of 22 normative documents yielded 16 relevant documents including three international declarations, five guidelines, four European legislative documents, and four recommendations (see Table S2 and Figure 2).

Data extraction and validity assessment

Among the 85 retained publications three publications were systematic reviews, defined as evidence level II a (none were II b), 15 were non-systematic reviews (evidence level III), 24 cross-sectional studies (level IV b), 16 narrative reviews, and 27 expert opinions (evidence level V b). All 16 normative documents were found to be evidence level I.

Development and refinement of recommendations

Evidence was translated into draft recommendations. Themes identified were the following: guiding principles, ethics, paediatric principles, consent to paediatric research, paediatric data- and biobanks: operational principles, sharing of data and samples, commercialization,

and third party access. In an iterative process draft recommendations were reviewed and refined by consulting experts and the European SHARE panel.

Consensus meeting

A total of 21 recommendations were drafted, grouped into the domains of Guiding Principles (Recommendation 1 - 3), Ethics (Recommendation 4 -7), Paediatric Principles (Recommendation 8 and 9), Consent in Paediatric Research (Recommendation 10 - 14), Paediatric Data- and Biobanks: Operational Principles (Recommendation 15 and 16), Sharing of Data and Samples (Recommendation 17 - 19), and Commercialization and Third Party Access (Recommendation 20 and 21). Face-to-face discussion further refined all recommendations resulting in an agreement of >80% for all at the final consensus conference.

Recommendations

Guiding Principles

The 2006 European Regulation No 1901/2006 of the European Parliament and of the Council on Medicinal Products for Paediatric Use (Paediatric Regulation) for the first time mandated the development and submission of an investigation plan for children at early stages of drug development in Europe[17]. The regulation emphasized the specific needs of children and aimed to end their status as "therapeutic orphans"[17,18]. In 2009, the EU Council published an action plan for rare diseases strongly encouraging Europe-wide collaborative studies including establishing sustainable infrastructure such as registries and biobanks[2]. The plan mandated support for research training and sharing of tools and expertise across Europe. It emphasized the need for the development of European guidelines and recommendations for evaluation and treatment of rare diseases[2]. The 7th Framework Program of the EU for Research 1982/2006/EC, Technological Development and Demonstration Activities encouraged the investigator-driven development of collaborative research networks, further building of European research capacity, and sharing of data and specimens[19]. In 2013, the Biobanks and Biomolecular Resources European Research Infrastructure Consortium (BBMRI-ERIC) was charged with the development of the Europe-wide research infrastructure

of biobanks[3]. These general principles for collaborative paediatric research in Europe are captured in Recommendations 1 - 3 (Table 1).

Ethics

The 2008 International Ethical Guidelines for Epidemiological Studies prepared by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) defined that all proposals to conduct research in human subjects must be submitted for review of scientific merit and ethical acceptability to review committees. It specified that ethics committees should establish working rules regarding frequency of meetings, a quorum of members, decision-making procedures, and review of decisions. The guidelines specified that the committee should provide its rules to prospective investigators[20]. In 2014, the Regulation 536/2014 of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use (Clinical Trials Regulation) aimed to simplify and harmonize the administrative provisions of clinical trials in Europe[21]. It mandated the submission of a single application dossier to all the Member States concerned through a single submission portal. The regulation defined that member states were to determine the appropriate body to be involved in the assessment of the application and to organize the involvement of ethics committees within a specific timeline of the trial. It further specified that the designated ethics committee had to have appropriate expertise and membership to review the application[21]. Concepts of centralization, transparency, and organizational expertise of ethics committees are captured in Recommendations 4 - 7 (Table 1).

Paediatric Principles

The 1989 Convention on the Rights of the Child defined principles founded on respect for the dignity and worth of each child, regardless of race, colour, gender, language, religion, opinions, origins, wealth, birth status, or ability[12]. The Convention aimed to protect children, to help secure their basic needs, and to enhance the possibility of reaching their best potential[12,22]. The World Medical Association statement of the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects emphasised the

importance of special protection of vulnerable populations including children[23]. It specified that medical research with a vulnerable group such as children is only justified, if the research is responsive to the health needs and priorities and cannot be carried out in a non-vulnerable group[23]. The benefit of participating in a research study has to outweigh the potential risk[21]. The principle of minimal risk is a virtual standard for research in children[24]. Minimal risk is considered a risk that is similar to the child's risk in everyday life[22] and should not be greater than the risk attached to a routine medical examination[25]. The 2014 Clinical Trials Regulation specified that research in children should be performed out of necessity and a presumed benefit for the minor directly or for children with the same condition[21,24]. The principles of subsidiarity and the paediatric rule are captured in the Recommendations 8 and 9 (Table 1).

Consent in Paediatric Research

The 2008 CIOMS/WHO International Ethical Guidelines for Epidemiological Studies mandated that before undertaking research involving children the investigator must ensure that a parent or legal representative of each child has given permission. In addition, the agreement of each child (assent) has to be obtained to the extent of the child's capability[20]. It demands that the investigator must convey the information in language suitable to the individual child's level of understanding and abilities. The consent/assent process has to include provision of sufficient time and opportunities for clarification[20]. The 2009 Organization for Economic Co-Operation and Development (OECD) Guidelines on Human Biobanks and Genetic Research Databases suggested participants should be given a range of possible scopes of consent to choose from including broad consent to minimize potential risk of harm. In addition, the participant's right to withdraw from the research at any time has to be emphasized[26]. The 2016 Recommendation CM/Rec (2016)6 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin defined that re-consent has to be obtained, when a person attains capacity to consent[27]. It also mandated that clear policies should be in place ensuring communication of concerning findings that are relevant for the health of the persons – the so-called incidental findings[27]. While in adults based on the UNESCO International Declaration on Human Genetic Data the right of an individual to decide whether or not to be informed of the results of genetic

examinations should be respected[28], the importance to act in the best interest of minors may override this right in children[29]. Refusal to be informed about clinically relevant findings therefore represents a barrier for the participation of minors in research; parents cannot make the choice for their children not be informed about clinically relevant resultsh[29]. The concepts of consent/assent, withdrawal of consent, re-consenting, and incidental findings in paediatric research are captured in the Recommendations 10-14 (Table 1).

Paediatric Data- and Biobanks

The 2009 OECD Guidelines on Human Biobanks and Genetic Research Databases mandated that data- and biobanks should be governed by principles of transparency and accountability including a clear formulation of governance structure and responsibility for its management[26]. It also demanded that operators should have protocols and processes in place to protect participants' personal and medical information. The 2013 European Commission Implementing Decision of the Biobanking and Biomolecular Resources European Research Infrastructure Consortium(BBMRI-ERIC) was charged with establishing and operating a pan-European research infrastructure including improved interoperability of data- and biobanks[3]. It also mandated the implementation of quality management including standardized procedures and best practices. The 2016 Recommendation CM/Rec (2016)6 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin demanded safeguards to be put in place to ensure confidentiality at the time of collection, storage, and transfer of biological materials[27] . The 2016 Regulation 2016/679 of the European Parliament and the Council, the General Data Protection Regulation, mandated special protection of information originating from children[30]. The concepts of organisation and conduct of paediatric data- and biobanks are captured in the Recommendations 15-21 (Table 1).

Discussion

The SHARE initiative developed the first European recommendations for collaborative, paediatric research including biobanking for children with rheumatic diseases. A comprehensive systematic literature review including European legislative documents and an iterative consensus procedure was completed. A total of 21 recommendations were developed, refined, agreed on by expert clinicians in childhood disease, methodologists, paediatric researchers, and content experts of paediatric ethics and legislation, partnered with patient representatives. These recommendations will provide a robust framework for collaborative European research in rare childhood diseases in multicentre studies and the European Reference Networks (ERN) that are currently being created.

Transformative European research in childhood diseases increasingly requires Europe-wide collaborations. This is particularly important for rare diseases such as the entire spectrum of rheumatic diseases of childhood. The proposed framework of recommendations includes concepts of guidance and support for collaborative research teams. It advocates increasing the competency and transparency of a proposed centralized ethics committee review processes of childhood rare diseases, as successfully modelled by the 2014 European Regulation on Clinical Trials [21]. It provides evidence-based, structured guidance for all aspects of consent, data harmonization, and standardization of bio-specimen SOPs across Europe. This framework is the first of its kind. It was built upon a comprehensive review of published evidence, guidance of European leaders in ethics and law, and practical experience of leading paediatric researchers, and expert clinicians. Normative documents including ratified European laws and international declarations were reviewed and served as high-level evidence, an approach common to the area of ethics research, yet unfamiliar to medical researcher. Most importantly, the process has integrated the perspective of families living with childhood rare diseases. While being constructed in the context of the European Union funded research grant for paediatric rheumatic diseases, it is thought that it is likely to be transferrable to all collaborative childhood rare diseases research.

Research in children poses the unique challenge and requires the inclusion of specific considerations. Most importantly, children have the right of designated paediatric research to advance the understanding of childhood diseases and development of best therapies[31]. This right has to be balanced with the societal mandate to protect children from harm[12]. The

recommendations aim to strike this balance by including principles such as subsidiarity, the paediatric rule, the protection of minors, and the minimization of burden[22]. Special considerations were given to the integration of minors in the consenting process[32]. While consent is obtained from the legal guardian, minors have to be appropriately informed and have to have a voice in the decision making process[33]. It was emphasised that consent in paediatric research should be broad to minimize harm and that re-consenting is mandatory when minors reach legal age[27]. The possibility of clinically relevant, actionable incidental findings has to be taken into account[34]. Distinctly different from research in adults, refusal to be informed about these findings has to be considered an exclusion criterion for paediatric research study participation[29].

There are several limitations to the study and its results. The key limitation is the generalizability beyond Europe. Published literature and normative documents applicable to the European context only informed the recommendation development. The transferability into another cultural context such as North or South America has to be explored. When aiming so, the literature search and evidence synthesis would have to include publications and most importantly normative documents beyond Europe. In addition, the expert team had a content and method focus on childhood rheumatic diseases. In order to increase the generalizability care researchers, patients and families with a spectrum of other conditions including common and rare, acute and chronic illnesses would need to be part of the process. The transferability to other childhood diseases could then be tested; recommendations may require additional specifications when applied to a different disease context. However, it appears that principles captured in the proposed set of recommendations are widely generalizable across childhood diseases.

The SHARE initiative enabled the development of the first recommendations for Paediatric Rheumatology collaborative research including data- and biobanking and sharing across borders. These recommendations provide strong support for an urgently needed European legislative framework and evidence-based guidance for its implementation. Children with rheumatic conditions and the many others suffering from rare diseases should no longer be left behind when life-changing research discoveries can be made.

Figure legends

Figure 1

Modified hierarchy of evidence pyramid for inclusion of normative documents

Legend: The pyramid depicting the hierarchy of evidence was modified with guidance of the Cochrane collaboration to enable the inclusion of all available scientific evidence and international normative documents in the systematic review.

Figure 2

Literature selection flow chart

Legend: The search included the following MESH-terms: data collection, ethics, biological specimen banks, confidentiality, informed consent by minors, specimen handling, quality improvement, and jurisprudence. In addition, the following subheadings were used: legislation, classification, methods, organization, administration, standards, and instrumentation. The search was limited to literature relevant to the paediatric age group (0 to 18 years of age) and to Europe.

Search strategy

((((((("Data Collection/ethics"[Mesh] OR "Data Collection/legislation and jurisprudence"[Mesh]))) OR ((((("Ethics/classification"[Mesh] OR "Ethics/ethics"[Mesh] OR "Ethics/legislation and jurisprudence"[Mesh] OR "Ethics/methods"[Mesh] OR "Ethics/organization and administration"[Mesh] OR "Ethics/standards"[Mesh]))) OR ethics)) AND (("Biological Specimen Banks/classification"[Mesh] OR "Biological Specimen Banks/ethics"[Mesh] OR "Biological Specimen Banks/instrumentation"[Mesh] OR "Biological Specimen Banks/legislation and jurisprudence"[Mesh] OR "Biological Specimen Banks/methods"[Mesh] OR "Biological Specimen Banks/organization and administration"[Mesh] OR "Biological Specimen Banks/standards"[Mesh])))) OR (((("Confidentiality/ethics"[Mesh] OR "Confidentiality/legislation and jurisprudence"[Mesh] OR "Confidentiality/organization and administration"[Mesh] OR "Confidentiality/standards"[Mesh]))) AND (("Biological Specimen

Banks/classification"[Mesh] OR "Biological Specimen Banks/ethics"[Mesh] OR "Biological Specimen Banks/instrumentation"[Mesh] OR "Biological Specimen Banks/legislation and jurisprudence"[Mesh] OR "Biological Specimen Banks/methods"[Mesh] OR "Biological Specimen Banks/organization and administration"[Mesh] OR "Biological Specimen Banks/standards"[Mesh])))) OR (("Informed Consent By Minors/ethics"[Mesh] OR "Informed Consent By Minors/legislation and jurisprudence"[Mesh] OR "Informed Consent By Minors/organization and administration"[Mesh] OR "Informed Consent By Minors/standards"[Mesh]))) OR ((((((("Specimen Handling/ethics"[Mesh] OR "Specimen Handling/legislation and jurisprudence"[Mesh]))) OR (("Specimen Handling/standards"[Majr]) AND "Quality Improvement"[Mesh])) OR (("Specimen Handling"[Mesh]) AND "Ethics"[Mesh])) OR (("Jurisprudence"[Majr]) AND "Specimen Handling"[Majr])) OR ((("Specimen Handling"[Majr]) And ("legislation and jurisprudence" [Subheading]))) OR (("Specimen Handling"[Majr]) AND "ethics" [Subheading])))) OR (("Data Collection/ethics"[Majr:NoExp] OR "Data Collection/legislation and jurisprudence"[Majr:NoExp]))

Table 1

Recommendations for collaborative paediatric research including biobanking in Europe

Text of recommendations	Justification	Evidence level	Strength of recommen-dation	Agree-ment
Guiding Principles				
Recommendation 1: Advancing Care and Discovery Research in children should be supported including international, multi-centre data collection and banking and transfer of biological specimens. Collaboration enables discovery in paediatric diseases and care advancement for children, in particular for those with rare diseases.	Discovery and care advancement in paediatric diseases requires collaborative longitudinal research projects of international scale in order to include sufficient numbers of participants and generate robust scientific data. The international collaborative collection, storage, and sharing of human biological material and associated clinical information reduce the overall burden of sampling for patients and researchers enabling sustained, high-quality research[2,17,18,22,33,35].	I	B	100%
Recommendation 2: Enabling Support Paediatric researchers should be offered research training opportunities, access to mentorship and guidance, protected time, and financial support to conduct paediatric research. Institutional resources for research protocol development, translation services, ethics submission, and research conduct should be made available.	The complexity of collaborative paediatric diseases research and the heterogeneity of rules, regulations, and processes within and across European countries mandate researchers to develop distinct skill sets and content knowledge. Focused, comprehensive training, institutional assistance, and guidance partnered with financial and other support will enable researchers to overcome the disproportionally challenging barriers towards successful multi-national paediatric diseases research requiring sample and data	I	B	100%

	collection [2,20,28,36-38].			
Recommendation 3: Supportive Legislative Framework A supportive legislative framework for international collaborating biobanks is lacking. A framework (WHO, ICH, EMA, FDA, other) should be implemented to overcome legal and ethical barriers in international research. An international binding shipment and custom agreement for biological samples should be established.	The regulatory requirements for paediatric biobanking vary significantly between European countries. This dramatically complicates the implementing of international paediatric diseases biobanks. A unified European framework should be developed and implemented in order to facilitate the international sharing of precious paediatric biospecimen and enable life-saving discoveries [3,24,33,37,39-42].	II	B	100%
Ethics				
Recommendation 4: Centralized Ethics All international collaborative paediatric research should be reviewed by central European Ethics Committees. All auxiliary studies require additional review and approval. The review has to capture all ethical principles including privacy rights.	Designated and highly qualified, independent, and centralized Ethics Committees should serve as Competent Authority for paediatric research. Subsequent, auxiliary studies should be reviewed by the same committee. The resulting single ethics vote captures the highest ethical principles and privacy standards. Subsequently National Ethics Committee reviews are solely tasked with evaluating cultural appropriateness [20,21,23,25-27,33,41,43].	I	B	94%
Recommendation 5: Standardization and Transparency All collaborative paediatric research applications in the European Community should be filed in a standardized format and be submitted to a	The current necessity of multiple ethics applications, the large variability in the submitting formats, and the lack of transparency of the reviewing process hinder collaborative paediatric research within the EU. A	I	B	100%

central electronic application portal. Following submission the review process should be transparent and electronically traceable.	standardized submission and approval process through a central application portal as implemented in the EU portal for all clinical trials will overcome this barrier and facilitate research and care advancement [21].			
Recommendation 6: Central Competency The European Central Ethics Application Board should rapidly assess all multicentre applications for meeting formal EU-standards. All applications including timelines should be tracked in a central repository. The application should be transferred to the applicant's designated National Ethics Committee for Paediatric Research and Biobanking and undergo review including compliance with the specific ethical principles. After sign off, the other participating National Ethics Committees should rapidly adopt the decision.	The standardization of application requirements and a unified primary, central review process overcomes barriers by simplifying the process while increasing the quality in accordance to the European regulation on clinical trials on medicinal products for human use (Clinical Trials Regulation)[21,44].	I	B	100%
Recommendation 7(1): Membership expertise Each National Ethics Committee for Paediatric Research and Biobanking should operate according to uniform standards. Membership: Each Committee has to include independent experts in paediatric research, lay members (non-professionals including patient	The ethics committee review of collaborative paediatric research studies and biobanking requires specific expertise reflected in its membership: Paediatricians should provide advice on clinical, ethical, and psychosocial aspects of research in minors. Lay members should offer support evaluating individual and societal impact of the proposed research. The review of genetic	I	A	94%

/ parent organizations or community advocates) and those with specific content expertise including genetics to review specific applications when appropriate.	studies mandates an additional content expert for guidance [20,21,25,44-46].			
Recommendation 7(2): Support and Clarity Ethics application: Each Committee should provide direct assistance, clear instructions, and training courses to support the researcher. Instructions and applications should be written in a simple, universally understood language. Fees: Administrative fees should exclusively be charged in non-academic research; if charged, they should not constitute an obstacle.	Administrative support, training opportunities, and transparent, simple instructions will help facilitate the paediatric research ethics application. For investigator initiated, non-commercial studies fees should not constitute a barrier to research. Fees should be set solely on the basis of cost recovery principles and be reduced or waived when appropriate [20,21,28,47].	I	A	100%
Paediatric Principles				
Recommendation 8: Subsidiarity A study that will produce generalizable results across all age groups should preferentially be performed in adults.	Adults should be primarily included in research studies, since they are capable of giving truly informed consent. Children are a vulnerable population and need protection. Generalizable research has to be conducted in adults capable to consent [20,22,23,25,27,33,41,42,44].	I	A	88%
Recommendation 9: Paediatric Rule Children should receive special	Children are a vulnerable population. The potential risks including privacy risks related to genetic information, physical	I	A	100%

protection when included in data and biobank studies.	and emotional harms, and disrespect of values should be minimized during sample collection and the duration of the research study. Justification is required when inviting vulnerable individuals to serve as research subjects, the risk should be minimal and the means of protecting rights and welfare must be strictly applied [20,22,23,25,27,33,42,43,45,48].			
Consent in Paediatric Research				
Recommendation 10: Integration of Minors Voluntary and age-appropriate informed consent/assent has to be obtained from legal guardians and/or minors as appropriate according to the international guidelines (ICH, WHO, others) before paediatric data and biospecimen can be collected and used for research. Minors should be integrated into the process of consent and those capable of forming an opinion and assessing the information given, should be asked to give assent or consent, as appropriate.	Children have the right to be included in research and benefit from research discoveries. All research mandates voluntary, informed consent given by a competent individual, who has received the necessary information and has adequately understood the information. The decision to participate has to be reached without coercion, undue influence or intimidation. Informed consent embodies the individual's freedom of choice and respects the individual's autonomy. Legal guardians may serve as proxies for minors, who do not have full capacity, in the consent process; children should be integrated in the consent process and their opinion and views have to be respected [12,20,22,23,25-27,31,33,43,46,49-53].	I	A	100%
Recommendation 11: Enabling Informed Consent All information given to the child and the legal guardian should be age appropriate,	The process of consenting must not be simply a ritual recitation of the contents of a written document. The information must be conveyed in language that suits the individual's level	I	B	100%

written, and presented by a competent person in the country's official language. Paediatric participants and legal guardians should be granted appropriate time to make and reconsider their decision. Withdrawal of consent should be possible at any time of the study.	of understanding. Parents/legal guardians and children must be given time and opportunity for discussion to make the decision without any pressure to consent. Participants should be informed that consent/assent can be withdrawn at any time. Exercising the right to withdraw cannot entail consequences in medical care services [20,22,23,25-27,43,46,48,49,52,54].			
Recommendation 12: Scope of Consent The scope of consent should preferably be broad. Broad consent should include future research opportunities, possibility to share samples and data with national and/or international research partners. Broad consent should include the possibility to re-contact participants. Consent forms need to be internationally harmonized to ensure international research projects. Consent forms have to include the possibility for specimen shipment and data transfer. Consenting should include the opportunity to opt out of certain aspects of research.	Broad consent reduces the burden for participants as it avoids the need for re-sampling of biospecimen and re-collection of data in addition to the need for re-consenting. Broad consent avoids the need to re-contact and re-consent participants, which may represent a significant barrier to conducting research. It allows for novel research to be conducted that had not been conceptualized at the time of the initial study. Permission for data and specimen transfer should be included in the harmonized consent forms. A governance specification and an opt-out option have to be included enabling participants to limit the use of their specimens and data to distinct research questions [22,26,27,30,37,43,45,48,55-57].	I	B	100%
Recommendation 13: Re-consenting Paediatric participants that have previously only given assent should be re-contacted for consent to an ongoing study when reaching legal age.	At time of reaching legal age the formal legal status of the participant changes. This mandates obtaining re-consent since the initial consent was not obtained from the minor and therefore has limited temporal	I	A	88%

Researchers should make considerable effort to re-contact participants for further use of data and samples. The ethics committee should evaluate the option of further use of data and sample, if participants are not reachable.	scope. Allowing the competent child a right to withdraw materials given into the biobank by proxy consent is consistent with the idea of a child's "right to an open future", which states that choices made for a child when being a minor should not preclude the right to make decisions when reaching legal age. The former minor has now full autonomy and is now able to oversee the dimension of the research and can give informed consent for ongoing research generated from databases and biobanks. In case the participant cannot be reached, the researcher should seek advice from the ethics committee for further use of data and samples [18,21,22,26,27,48,58,59].			
Recommendation 14: **Incidental Findings** Researchers should partner with expert health care providers and inform patients and legal guardians about clinically relevant results. Participant's refusal to be informed about clinically relevant results represents an exclusion criterion.	In adults the principle of autonomy and the individual right "to know or not to know" defines the extent to which researchers should inform participants including children and their legal guardians about clinically relevant results detected in research studies. In paediatric studies, the proxy consent does not cover this decision. Here, researchers have a moral duty to inform minor participants and their legal guardians about clinically relevant results that mandate action including research result and incidental findings. Findings should be communicated by an expert clinician [20,22,23,25,27-	I	B	100%

	[29,33,42,43,60].			
Paediatric Data and Biobanks: Operational Principles				
Recommendation 15: Organizational Framework The organizational frameworks for collaborative paediatric data- and biobanks must include a governance structure. Terms of transparency, fair access to data and samples including ownership, authorship of research publications, payment, and reciprocity of sample sharing should be defined. Principles of interoperability should be followed. Data- and /or material transfer agreements should be elaborated and signed between research partners. Researchers should develop a long-term plan for sustainability. Biobanks should be captured in a central electronic tracking system.	An organizational framework prevents ethical and legal conflicts, enables long-term collaborations between participating researchers. The development and endorsement of standards enables higher research interoperability. Transparency of the framework and its policies is necessary for biobanks in all levels. Standardized design and harmonization of data fields enables interoperability between biobanks. A governance structure and a long-term sustainability plan will ensure public trust and long benefits. A central registry for European biobanks will not only reduce the burden of repeated sample collection but also helps to use existing resources in the most efficient way [3,21,26-28,33,37,43,57,61].	I	B	100%
Recommendation 16: Sampling Non-invasive sampling approaches should be preferentially used in children. Standard operating procedures (SOPs) of paediatric sample collection, processing, pre-analytic handling, and shipment should be defined and observed to ensure high quality specimen handling.	The Paediatric Rule mandates minimal invasive sampling, which may result in small quantities of biospecimen and may require designated, harmonized SOPs. Processing of paediatric biospecimen and capture of paediatric data samples should include necessary measures to ensure the accuracy, reliability, quality, and security [20,25,27,28,41,46,57,61,62].	I	B	100%)

Sharing of Data and Samples				
Recommendation 17: Data Harmonization Collaborative databanks should built on available *instruments* of data harmonization, standardized access to data, define measures of high data quality including data dictionaries, and regulate data transfer.	Harmonization of data fosters the interoperability of systems and facilitates the exchange of scientific data. High quality standards enable the possibility of international collaborative research with health related benefits for future generations. Quality assurance measures should be implemented, including conditions to ensure appropriate security and confidentiality during establishment of the collection, storage, use and, where appropriate, transfer of data and materials [3,26-28,30,33,57,61,63].	I	A	100%
Recommendation 18: **Data Protection** Researchers should implement a state-of-the-art data and sample protection system. Secure coding of data and samples should ensure confidentiality while enabling withdrawal of consent, re-consenting, and notification of clinically relevant results. Secure data-sample linkage systems should be established.	Researchers are custodians of personal data and biospecimen. They are responsible for establishing a system of secure safeguards for privacy, confidentiality, and legitimate access. While using anonymous data and samples is the best way to protect personal information, it is not feasible in paediatric research as it limits the researchers' ability to act on withdrawal of consent, the need for re-consenting and the detection, and notification of clinically relevant results. All data handling has to follow the standards of the EU General Data Protection Regulation [20,26,27,30,33,37,46,57,61,63].	I	A	100%
Recommendation 19: Standardization of Transfer Specimen transfer should include standardized packaging and labelling,	Standardization of shipment in accordance with international regulations and laws including all accompanying documents ensures a safe and confidential transfer of biological materials	I	B	100%

accompanying transfer documentation, customs regulations, and sample tracking. The consent form must include the agreement to share data and samples.	across borders. A documented agreement between the sender of the biological materials and the recipient should be signed. The patient's agreement of data and specimen transfer has to be obtained and shared [26-28,35,37].			
Commercialization and Third Party Access				
Recommendation 20: Fees and Incentives Biobanks should enable research to improve medical knowledge. Provision of data and samples should be free; shipment and processing costs should be covered by the requesting research team. Participants or their parents should not receive payment.	Responsible sharing of biospecimen and data should be guided by the principle of the "Universal Declaration of Human Rights, 1948", which grants every individual the right to „share in scientific advancement and its benefits". In fact, the Council of Europe states that sharing of all knowledge and distribution of materials will be obligatory. Collaborative paediatric research aims to maximize discoveries by sharing of resources, data, and samples. Financial incentives should be avoided. The operators of data and biobanks must ensure that any stratified access or fee policies are fair, transparent, and do not inhibit research [20,25,26,28,33,37,39,61,64,65].	I	A	100%
Recommendation 21: Third Parties Researchers have to obtain ethics approval before giving patient data or sample access to third parties. Continuous education of the public about biobanks is important to retain public trust in research.	The autonomy principle mandates that a patient has to give consent to any sharing of data and biospecimen. A researcher therefore should not share any data or specimens with third parties unless the patient permits such submission and an ethics approval was obtained. The most important prerequisite for successful biobank related research is ensuring the public	I	A	100%

	trust. This can be achieved through continuous education of people and protection of privacy [18,20,25,26,30,33,39,43,45].			

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Title

Recommendations for collaborative paediatric research including biobanking in Europe – A Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) Initiative

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Abstract

Objectives: Innovative research in childhood rheumatic diseases mandates international collaborations. However, researchers struggle with significant regulatory heterogeneity; an enabling EU-wide framework is missing. The aims of the study were to systematically review the evidence for best practice and to establish recommendations for collaborative research.

Methods: The Paediatric Rheumatology European SHARE project enabled a scoping review and expert discussion, which then informed ~~a~~ the systematic literature review. Published evidence was synthesized; recommendations were drafted. An iterative review process and consultations with Ethics Committees and European experts for ethical and legal aspects of paediatric research refined the recommendations. SHARE experts and patient representatives vetted the proposed recommendations at a consensus meeting using Nominal Group Technique. Agreement of 80% was mandatory for inclusion.

Results: The systematic literature review returned 1319 records. A total of 223 full-text publications plus 22 international normative documents were reviewed; 85 publications and 16 normative documents were included. A total of 21 recommendations were established including general principles (1-3), ethics (4-7), paediatric principles (8 and 9), consent to paediatric research (10 -14), paediatric data- and biobanks (15 and 16), sharing of data and samples (17 - 19), and commercialization and third parties (20 and 21). The refined recommendations resulted in an agreement of >80% for all recommendations.

Conclusions: The SHARE initiative established the first recommendations for Paediatric Rheumatology collaborative research across borders in Europe. These provide strong support for an urgently needed European framework and evidence-based guidance for its implementation. Such changes will promote research in children with rheumatic diseases.

Introduction

Paediatric rheumatic diseases are rare and often devastating; advancing knowledge and improving care and outcomes of affected children mandates research collaborations across national borders [1-3]. Across Europe, several national innovative research teams have made substantial contributions to developing clinical tools, biomarkers, and imaging strategies for children with rheumatic diseases. Their evaluation and implementation mandates international patient cohorts and research partnerships given that some paediatric rheumatic diseases have incidences as low as one per million.

The European community strongly encourages collaborative international research and funded the “Single Hub and Access point for paediatric Rheumatology in Europe (SHARE)" initiative, which aims to optimize care and research for children with rheumatic diseases across Europe[4-8]. A key task was the identification of barriers between nations for collaborative Paediatric Rheumatology research. Currently, researchers funded to conduct important studies struggle with the substantial heterogeneity within and across European countries in all areas of rare diseases research. These include ethics approval process, consent and assent, formal frameworks for data and sample collection and sharing, and aspects of third party data and sample access. Currently there is no EU-wide framework facilitating the conduct of collaborative rare diseases research[9].

Therefore the aims of the study were to synthesize the evidence for best practice in paediatric rheumatic diseases research and to develop recommendations to enable research collaborations including data- and biobanking across Europe.

Methods

Scoping review and expert consultation

A scoping review ~~focussing~~ on collaborative paediatric research was conducted identifying key themes. In addition, major stakeholders including ethics committee members, European Paediatric Rheumatology researchers, and patients with rare diseases were asked to provide input regarding their perspectives on research and its barriers and challenges using structured interviews by surveys, phone, and in-person. The group identified key themes and constructed an evaluative framework including a modification of the evidence ranking system supported by the Cochrane group (Figure 1).

Systematic review

Search strategy and selection criteria

A systematic literature review anchored in the identified key themes was performed and reported according to the standards of the "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA)" guidelines[10,11]. This systematic search of the literature aimed to identify studies of ~~focussing on~~ all aspects of paediatric research in Europe. These were specified in MESH terms and subheadings including data collection, ethics, biological specimen banks, confidentiality, informed consent by minors, specimen handling, jurisprudence, quality improvement, legislation, classification, methods, organization, administration, standards, and instrumentation. The search was performed in the electronic databases PubMed and Web of Science on 14th May 2014. The search was limited to articles published in English and ~~focussing on~~ children and adolescents (ages 0-18 years); the search period was set between January 1989 and April 2014, guided by the publication date of the United Nation's Convention on the Rights of the Child[12]. In addition to the electronic literature search, a manual review of the references of all relevant publications and international and European normative documents was conducted. Articles were excluded, if the content was not related to children and adolescents, it did not apply to the European context, or to any aspect of collaborative paediatric research.

Data extraction and validity assessment

The remaining full-text articles were reviewed by a panel of experts, graded by two independent researchers, and reconciled by a third using predefined scoring instruments for the different study and publication types as appropriate[13,14]. The following variables were abstracted: reference, year of publication, authors, country of focus, and contribution to the themes. Levels of evidence and strength of recommendations were determined using an adjusted framework for grading scientific evidence in order to account for normative documents including declarations, regulations, guidelines, and legislative documents[15].

Development and refinement of recommendations

Grouped by distinct themes, the evidence was synthesized; additional domains were developed including public opinion on paediatric research, guidelines, and jurisdiction. Recommendations were drafted. In-depth discussion, iterative reviews, and adjustments of the recommendations were completed with ethics committee staff members and international content experts in paediatric ethics (KH) and legislation (DS). The draft version of the recommendations was sent to all SHARE experts in an online survey format for review and revision. All suggestions were integrated and additional recommendations were drafted; the revised documents were re-distributed to the experts for review and evaluation of agreement.

Consensus meeting

The proposed and reviewed recommendations were presented to the SHARE expert committee and patient representatives during a face-to-face consensus meeting in Rome, Italy, and discussed in-depth using Nominal Group Technique[16]. Recommendations were accepted by reaching agreement above 80%.

Results

Scoping review and expert consultation

The key themes of collaborative paediatric research and biobanking in Paediatric Rheumatology were identified. These included ethics, legislation, consent, scope of consent, confidentiality, anonymisation, sample and data collection, handling, and storage. These were translated into search terms to inform the evidence synthesis.

Systematic literature review

The initial search returned 7347 records, of which 6503 had to be excluded. Ultimately, 1319 publications including 844 from PubMed and 475 papers from the Web of Science Core Collection were identified. After removing 31 duplicates, a total of 1288 records were manually reviewed for title and abstract excluding 1065. Full-text assessment of 223 papers resulted in exclusion of 161. A total of 62 publications plus an additional 23 identified by targeted hand-search from references resulted in 85 papers to be included (see Table S1). A full-text review of 22 normative documents yielded 16 relevant documents including three international declarations, five guidelines, four European legislative documents, and four recommendations (see Table S2 and Figure 2).

Data extraction and validity assessment

Among the 85 retained publications three publications were systematic reviews, defined as evidence level II a (none were II b), 15 were non-systematic reviews (evidence level III), 24 cross-sectional studies (level IV b), 16 narrative reviews, and 27 expert opinions (evidence level V b). All 16 normative documents were found to be evidence level I.

Development and refinement of recommendations

Evidence was translated into draft recommendations. Themes identified were the following: guiding principles, ethics, paediatric principles, consent to paediatric research, paediatric data- and biobanks: operational principles, sharing of data and samples, commercialization,

and third party access. In an iterative process draft recommendations were reviewed and refined by consulting experts and the European SHARE panel.

Consensus meeting

A total of 21 recommendations were drafted, grouped into the domains of Guiding Principles (Recommendation 1 - 3), Ethics (Recommendation 4 -7), Paediatric Principles (Recommendation 8 and 9), Consent in Paediatric Research (Recommendation 10 - 14), Paediatric Data- and Biobanks: Operational Principles (Recommendation 15 and 16), Sharing of Data and Samples (Recommendation 17 - 19), and Commercialization and Third Party Access (Recommendation 20 and 21). Face-to-face discussion further refined all recommendations resulting in an agreement of >80% for all at the final consensus conference.

Recommendations

Guiding Principles

The 2006 European Regulation No 1901/2006 of the European Parliament and of the Council on Medicinal Products for Paediatric Use (Paediatric Regulation) for the first time mandated the development and submission of an investigation plan for children at early stages of drug development in Europe[17]. The regulation emphasized the specific needs of children and aimed to end their status as "therapeutic orphans"[17,18]. In 2009, the EU Council published an action plan for rare diseases strongly encouraging Europe-wide collaborative studies including establishing sustainable infrastructure such as registries and biobanks[2]. The plan mandated support for research training and sharing of tools and expertise across Europe. It emphasized the need for the development of European guidelines and recommendations for evaluation and treatment of rare diseases[2]. The 7th Framework Program of the EU for Research 1982/2006/EC, Technological Development and Demonstration Activities encouraged the investigator-driven development of collaborative research networks, further building of European research capacity, and sharing of data and specimens[19]. In 2013, the Biobanks and Biomolecular Resources European Research Infrastructure Consortium (BBMRI-ERIC) was charged with the development of ~~a~~ the Europe-wide research

infrastructure of biobanks[3]. These general principles for collaborative paediatric research in Europe are captured in Recommendations 1 - 3 (Table 1).

Ethics

The 2008 International Ethical Guidelines for Epidemiological Studies prepared by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) defined that all proposals to conduct research in human subjects must be submitted for review of scientific merit and ethical acceptability to review committees. It specified that ethics committees should establish working rules regarding frequency of meetings, a quorum of members, decision-making procedures, and review of decisions. The guidelines specified that the committee should provide its rules to prospective investigators[20]. In 2014, the Regulation 536/2014 of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use (Clinical Trials Regulation) aimed to simplify and harmonize the administrative provisions of clinical trials in Europe[21]. It mandated the submission of a single application dossier to all the Member States concerned through a single submission portal. The regulation defined that member states were to determine the appropriate body to be involved in the assessment of the application and to organize the involvement of ethics committees within a specific timeline of the trial. It further specified that the designated ethics committee had to have appropriate expertise and membership to review the application[21]. Concepts of centralization, transparency, and organizational expertise of ethics committees are captured in Recommendations 4 - 7 (Table 1).

Paediatric Principles

The 1989 Convention on the Rights of the Child defined principles founded on respect for the dignity and worth of each child, regardless of race, colour, gender, language, religion, opinions, origins, wealth, birth status, or ability[12]. The Convention aimed to protect children, to help secure their basic needs, and to enhance the possibility of reaching their best potential[12,22]. The World Medical Association statement of the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects emphasised the

importance of special protection of vulnerable populations including children[23]. It specified that medical research with a vulnerable group such as children is only justified, if the research is responsive to the health needs and priorities and cannot be carried out in a non-vulnerable group[23]. The benefit of participating in a research study has to outweigh the potential risk[21]. The principle of minimal risk is a virtual standard for research in children[24]. Minimal risk is considered a risk that is similar to the child's risk in everyday life[22] and should not be greater than the risk attached to a routine medical examination[25]. The 2014 Clinical Trials Regulation specified that research in children should be performed out of necessity and a presumed benefit for the minor directly or for children with the same condition[21,24]. The principles of subsidiarity and the paediatric rule are captured in the Recommendations 8 and 9 (Table 1).

Consent in Paediatric Research

The 2008 CIOMS/WHO International Ethical Guidelines for Epidemiological Studies mandated that before undertaking research involving children the investigator must ensure that a parent or legal representative of each child has given permission. In addition, the agreement of each child (assent) has to be obtained to the extent of the child's capability[20]. It demands that the investigator must convey the information in language suitable to the individual child's level of understanding and abilities. The consent/assent process has to include provision of sufficient time and opportunities for clarification[20]. The 2009 Organization for Economic Co-Operation and Development (OECD) Guidelines on Human Biobanks and Genetic Research Databases suggested participants should be given a range of possible scopes of consent to choose from including broad consent to minimize potential risk of harm. In addition, the participant's right to withdraw from the research at any time has to be emphasized[26]. The 2016 Recommendation CM/Rec (2016)6 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin defined that re-consent has to be obtained, when a person attains capacity to consent[27]. It also mandated that clear policies should be in place ensuring communication of concerning findings that are relevant for the health of the persons – the so-called incidental findings[27]. While in adults based on the UNESCO International Declaration on Human Genetic Data the right of an individual to decide whether or not to be informed of the results of genetic

examinations should be respected[28], the importance to act in the best interest of minors may override this right in children[29]. ~~Refusal to be informed about incidental findings therefore represents a barrier for the participation of minors in~~ Refusal to be informed about clinically relevant findings therefore represents a barrier for the participation of minors in research; parents cannot make the choice for their children not be informed about clinically relevant results~~researc~~h[29]. The concepts of consent/assent, withdrawal of consent, re-consenting, and incidental findings in paediatric research are captured in the Recommendations 10-14 (Table 1).

Paediatric Data- and Biobanks

The 2009 OECD Guidelines on Human Biobanks and Genetic Research Databases mandated that data- and biobanks should be governed by principles of transparency and accountability including a clear formulation of governance structure and responsibility for its management[26]. It also demanded that operators should have protocols and processes in place to protect participants' personal and medical information. The 2013 European Commission Implementing Decision of the Biobanking and Biomolecular Resources European Research Infrastructure Consortium(BBMRI-ERIC) was charged with establishing and operating a pan-European research infrastructure including improved interoperability of data- and biobanks[3]. It also mandated the implementation of quality management including standardized procedures and best practices. The 2016 Recommendation CM/Rec (2016)6 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin demanded safeguards to be put in place to ensure confidentiality at the time of collection, storage, and transfer of biological materials[27] . The 2016 Regulation 2016/679 of the European Parliament and the Council, the General Data Protection Regulation, mandated special protection of information originating from children[30]. The concepts of organisation and conduct of paediatric data- and biobanks are captured in the Recommendations 15-21 (Table 1).

Discussion

The SHARE initiative developed the first European recommendations for collaborative, paediatric research including biobanking for children with rheumatic diseases. A comprehensive systematic literature review including European legislative documents and an iterative consensus procedure was completed. A total of 21 recommendations were developed, refined, agreed on by expert clinicians in childhood disease, methodologists, paediatric researchers, and content experts of paediatric ethics and legislation, partnered with patient representatives. These recommendations will provide a robust framework for collaborative European research in rare childhood diseases in multicentre studies and the European Reference Networks (ERN) that are currently being created.

Transformative European research in childhood diseases increasingly requires Europe-wide collaborations. This is particularly important for rare diseases such as the entire spectrum of rheumatic diseases of childhood. The proposed framework of recommendations includes concepts of guidance and support for collaborative research teams. It advocates increasing the competency and transparency of a proposed centralized ethics committee review processes of childhood rare diseases, as successfully modelled by the 2014 European Regulation on Clinical Trials [21]. It provides evidence-based, structured guidance for all aspects of consent, data harmonization, and standardization of bio-specimen SOPs across Europe. This framework is the first of its kind. It was built upon a comprehensive review of published evidence, guidance of European leaders in ethics and law, and practical experience of leading paediatric researchers, and expert clinicians. Normative documents including ratified European laws and international declarations were reviewed and served as high-level evidence, an approach common to the area of ethics research, yet unfamiliar to medical researcher. Most i~~I~~mportantly, the process ~~it~~ has integrated the perspective of families living with childhood rare diseases. While being constructed in the context of ~~a~~ the European Union funded research grant for paediatric rheumatic diseases, it is thought that it is likely to be transferrable to all collaborative childhood rare diseases research.

Research in children poses ~~a~~ the unique challenge and requires the inclusion of specific considerations. Most importantly, children have the right of designated paediatric research to advance the understanding of childhood diseases and development of best therapies[31]. This right has to be balanced with the societal mandate to protect children from harm[12]. The

recommendations aim to strike this balance by including principles such as subsidiarity, the paediatric rule, the protection of minors, and the minimization of burden[22]. Special considerations were given to the integration of minors in the consenting process[32]. While consent is obtained from the legal guardian, minors have to be appropriately informed and have to have a voice in the decision making process[33]. It was emphasised that consent in paediatric research should be broad to minimize harm and that re-consenting is mandatory when minors reach legal age[27]. The possibility of clinically relevant, actionable incidental findings has to be taken into account[34]. Distinctly different from research in adults, refusal to be informed about these findings has to be considered an exclusion criterion for paediatric research study participation[29].

There are several limitations to the study and its results. The key limitation is the generalizability beyond Europe. Published literature and normative documents applicable to the European context only informed the recommendation development. The transferability into another cultural context such as North or South America has to be explored. When aiming so, the literature search and evidence synthesis would have to include publications and most importantly normative documents beyond Europe. In addition, ~~The~~ the expert team had a content and method focus on childhood rheumatic diseases. In order to increase the generalizability care researchers, patients and families with a spectrum of other conditions including common and rare, acute and chronic illnesses would need to be part of the process. The transferability to other childhood diseases c~~sh~~ould then be tested; recommendations may require additional specifications when applied to a different disease context. However, it appears that principles captured in the proposed set of recommendations are widely generalizable across childhood diseases.

The SHARE initiative enabled the development of the first recommendations for Paediatric Rheumatology collaborative research including data- and biobanking and sharing across borders. These recommendations provide strong support for an urgently needed European legislative framework and evidence-based guidance for its implementation. Children with rheumatic conditions and the many others suffering from rare diseases should no longer be left behind when life-changing research discoveries can be made.

Figure legends

Figure 1

Modified hierarchy of evidence pyramid for inclusion of normative documents

Legend: The pyramid depicting the hierarchy of evidence was modified with guidance of the Cochrane collaboration to enable the inclusion of all available scientific evidence and international normative documents in the systematic review.

Figure 2

Literature selection flow chart

Legend: The search included the following MESH-terms: data collection, ethics, biological specimen banks, confidentiality, informed consent by minors, specimen handling, quality improvement, and jurisprudence. In addition, the following subheadings were used: legislation, classification, methods, organization, administration, standards, and instrumentation. The search was limited to literature relevant to the paediatric age group (0 to 18 years of age) and to Europe.

Search strategy

((((((("Data Collection/ethics"[Mesh] OR "Data Collection/legislation and jurisprudence"[Mesh]))) OR ((((((("Ethics/classification"[Mesh] OR "Ethics/ethics"[Mesh] OR "Ethics/legislation and jurisprudence"[Mesh] OR "Ethics/methods"[Mesh] OR "Ethics/organization and administration"[Mesh] OR "Ethics/standards"[Mesh]))) OR ethics)) AND (("Biological Specimen Banks/classification"[Mesh] OR "Biological Specimen Banks/ethics"[Mesh] OR "Biological Specimen Banks/instrumentation"[Mesh] OR "Biological Specimen Banks/legislation and jurisprudence"[Mesh] OR "Biological Specimen Banks/methods"[Mesh] OR "Biological Specimen Banks/organization and administration"[Mesh] OR "Biological Specimen Banks/standards"[Mesh])))) OR ((((("Confidentiality/ethics"[Mesh] OR "Confidentiality/legislation and jurisprudence"[Mesh] OR "Confidentiality/organization and administration"[Mesh] OR

"Confidentiality/standards"[Mesh]))) AND (("Biological Specimen Banks/classification"[Mesh] OR "Biological Specimen Banks/ethics"[Mesh] OR "Biological Specimen Banks/instrumentation"[Mesh] OR "Biological Specimen Banks/legislation and jurisprudence"[Mesh] OR "Biological Specimen Banks/methods"[Mesh] OR "Biological Specimen Banks/organization and administration"[Mesh] OR "Biological Specimen Banks/standards"[Mesh])))) OR (("Informed Consent By Minors/ethics"[Mesh] OR "Informed Consent By Minors/legislation and jurisprudence"[Mesh] OR "Informed Consent By Minors/organization and administration"[Mesh] OR "Informed Consent By Minors/standards"[Mesh]))) OR ((((((("Specimen Handling/ethics"[Mesh] OR "Specimen Handling/legislation and jurisprudence"[Mesh]))) OR (("Specimen Handling/standards"[Majr]) AND "Quality Improvement"[Mesh])) OR (("Specimen Handling"[Mesh]) AND "Ethics"[Mesh])) OR (("Jurisprudence"[Majr]) AND "Specimen Handling"[Majr])) OR ((((("Specimen Handling"[Majr]) And ("legislation and jurisprudence" [Subheading]))) OR (("Specimen Handling"[Majr]) AND "ethics" [Subheading])))))) OR (("Data Collection/ethics"[Majr:NoExp] OR "Data Collection/legislation and jurisprudence"[Majr:NoExp]))

Table 1

Recommendations for collaborative paediatric research including biobanking in Europe

Text of recommendations	Justification	Evidence level	Strength of recommen-dation	Agree-ment
Guiding Principles				
Recommendation 1: Advancing Care and Discovery Research in children should be supported including international, multi-centre data collection and banking and transfer of biological specimens. Collaboration enables discovery in paediatric diseases and care advancement for children, in particular for those with rare diseases.	Discovery and care advancement in paediatric diseases requires collaborative longitudinal research projects of international scale in order to include sufficient numbers of participants and generate robust scientific data. The international collaborative collection, storage, and sharing of human biological material and associated clinical information reduce the overall burden of sampling for patients and researchers enabling sustained, high-quality research[2,17,18,22,33,35].	I	B	100%
Recommendation 2: Enabling Support Paediatric researchers should be offered research training opportunities, access to mentorship and guidance, protected time, and financial support to conduct paediatric research. Institutional resources for research protocol development, translation services, ethics submission, and research conduct should be made available.	The complexity of collaborative paediatric diseases research and the heterogeneity of rules, regulations, and processes within and across European countries mandate researchers to develop distinct skill sets and content knowledge. Focused, comprehensive training, institutional assistance, and guidance partnered with financial and other support will enable researchers to overcome the disproportionally challenging barriers towards successful multi-national paediatric diseases research requiring sample and data	I	B	100%

	collection [2,20,28,36-38].			
Recommendation 3: Supportive Legislative Framework A supportive legislative framework for international collaborating biobanks is lacking. A framework (WHO, ICH, EMA, FDA, other) should be implemented to overcome legal and ethical barriers in international research. An international binding shipment and custom agreement for biological samples should be established.	The regulatory requirements for paediatric biobanking vary significantly between European countries. This dramatically complicates the implementing of international paediatric diseases biobanks. A unified European framework should be developed and implemented in order to facilitate the international sharing of precious paediatric biospecimen and enable life-saving discoveries [3,24,33,37,39-42].	II	B	100%
Ethics				
Recommendation 4: Centralized Ethics All international collaborative paediatric research should be reviewed by central European Ethics Committees. All auxiliary studies require additional review and approval. The review has to capture all ethical principles including privacy rights.	Designated and highly qualified, independent, and centralized Ethics Committees should serve as Competent Authority for paediatric research. Subsequent, auxiliary studies should be reviewed by the same committee. The resulting single ethics vote captures the highest ethical principles and privacy standards. Subsequently National Ethics Committee reviews are solely tasked with evaluating cultural appropriateness [20,21,23,25-27,33,41,43].	I	B	94%
Recommendation 5: Standardization and Transparency All collaborative paediatric research applications in the European Community should be filed in a standardized format and be submitted to a	The current necessity of multiple ethics applications, the large variability in the submitting formats, and the lack of transparency of the reviewing process hinder collaborative paediatric research within the EU. A	I	B	100%

central electronic application portal. Following submission the review process should be transparent and electronically traceable.	standardized submission and approval process through a central application portal as implemented in the EU portal for all clinical trials will overcome this barrier and facilitate research and care advancement [21].			
Recommendation 6: Central Competency The European Central Ethics Application Board should rapidly assess all multicentre applications for meeting formal EU-standards. All applications including timelines should be tracked in a central repository. The application should be transferred to the applicant's designated National Ethics Committee for Paediatric Research and Biobanking and undergo review including compliance with the specific ethical principles. After sign off, the other participating National Ethics Committees should rapidly adopt the decision.	The standardization of application requirements and a unified primary, central review process overcomes barriers by simplifying the process while increasing the quality in accordance to the European regulation on clinical trials on medicinal products for human use (Clinical Trials Regulation)[21,44].	I	B	100%
Recommendation 7(1): Membership expertise Each National Ethics Committee for Paediatric Research and Biobanking should operate according to uniform standards. Membership: Each Committee has to include independent experts in paediatric research, lay members (non-professionals including patient	The ethics committee review of collaborative paediatric research studies and biobanking requires specific expertise reflected in its membership: Paediatricians should provide advice on clinical, ethical, and psychosocial aspects of research in minors. Lay members should offer support evaluating individual and societal impact of the proposed research. The review of genetic	I	A	94%

/ parent organizations or community advocates) and those with specific content expertise including genetics to review specific applications when appropriate.	studies mandates an additional content expert for guidance [20,21,25,44-46].			
Recommendation 7(2): Support and Clarity Ethics application: Each Committee should provide direct assistance, clear instructions, and training courses to support the researcher. Instructions and applications should be written in a simple, universally understood language. Fees: Administrative fees should exclusively be charged in non-academic research; if charged, they should not constitute an obstacle.	Administrative support, training opportunities, and transparent, simple instructions will help facilitate the paediatric research ethics application. For investigator initiated, non-commercial studies fees should not constitute a barrier to research. Fees should be set solely on the basis of cost recovery principles and be reduced or waived when appropriate [20,21,28,47].	I	A	100%
Paediatric Principles				
Recommendation 8: Subsidiarity A study that will produce generalizable results across all age groups should preferentially be performed in adults.	Adults should be primarily included in research studies, since they are capable of giving truly informed consent. Children are a vulnerable population and need protection. Generalizable research has to be conducted in adults capable to consent [20,22,23,25,27,33,41,42,44].	I	A	88%
Recommendation 9: Paediatric Rule Children should receive special	Children are a vulnerable population. The potential risks including privacy risks related to genetic information, physical	I	A	100%

protection when included in data and biobank studies.	and emotional harms, and disrespect of values should be minimized during sample collection and the duration of the research study. Justification is required when inviting vulnerable individuals to serve as research subjects, the risk should be minimal and the means of protecting rights and welfare must be strictly applied [20,22,23,25,27,33,42,43,45,48].			
Consent in Paediatric Research				
Recommendation 10: Integration of Minors Voluntary and age-appropriate informed consent/assent has to be obtained from legal guardians and/or minors as appropriate according to the international guidelines (ICH, WHO, others) before paediatric data and biospecimen can be collected and used for research. Minors should be integrated into the process of consent and those capable of forming an opinion and assessing the information given, should be asked to give assent or consent, as appropriate.	Children have the right to be included in research and benefit from research discoveries. All research mandates voluntary, informed consent given by a competent individual, who has received the necessary information and has adequately understood the information. The decision to participate has to be reached without coercion, undue influence or intimidation. Informed consent embodies the individual's freedom of choice and respects the individual's autonomy. Legal guardians may serve as proxies for minors, who do not have full capacity, in the consent process; children should be integrated in the consent process and their opinion and views have to be respected [12,20,22,23,25-27,31,33,43,46,49-53].	I	A	100%
Recommendation 11: Enabling Informed Consent All information given to the child and the legal guardian should be age appropriate,	The process of consenting must not be simply a ritual recitation of the contents of a written document. The information must be conveyed in language that suits the individual's level	I	B	100%

written, and presented by a competent person in the country's official language. Paediatric participants and legal guardians should be granted appropriate time to make and reconsider their decision. Withdrawal of consent should be possible at any time of the study.	of understanding. Parents/legal guardians and children must be given time and opportunity for discussion to make the decision without any pressure to consent. Participants should be informed that consent/assent can be withdrawn at any time. Exercising the right to withdraw cannot entail consequences in medical care services [20,22,23,25-27,43,46,48,49,52,54].			
Recommendation 12: Scope of Consent The scope of consent should preferably be broad. Broad consent should include future research opportunities, possibility to share samples and data with national and/or international research partners. Broad consent should include the possibility to re-contact participants. Consent forms need to be internationally harmonized to ensure international research projects. Consent forms have to include the possibility for specimen shipment and data transfer. Consenting should include the opportunity to opt out of certain aspects of research.	Broad consent reduces the burden for participants as it avoids the need for re-sampling of biospecimen and re-collection of data in addition to the need for re-consenting. Broad consent avoids the need to re-contact and re-consent participants, which may represent a significant barrier to conducting research. It allows for novel research to be conducted that had not been conceptualized at the time of the initial study. Permission for data and specimen transfer should be included in the harmonized consent forms. A governance specification and an opt-out option have to be included enabling participants to limit the use of their specimens and data to distinct research questions [22,26,27,30,37,43,45,48,55-57].	I	B	100%
Recommendation 13: Re-consenting Paediatric participants that have previously only given assent should be re-contacted for consent to an ongoing study when reaching legal age.	At time of reaching legal age the formal legal status of the participant changes. This mandates obtaining re-consent since the initial consent was not obtained from the minor and therefore has limited temporal	I	A	88%

Researchers should make considerable effort to re-contact participants for further use of data and samples. The ethics committee should evaluate the option of further use of data and sample, if participants are not reachable.	scope. Allowing the competent child a right to withdraw materials given into the biobank by proxy consent is consistent with the idea of a child's "right to an open future", which states that choices made for a child when being a minor should not preclude the right to make decisions when reaching legal age. The former minor has now full autonomy and is now able to oversee the dimension of the research and can give informed consent for ongoing research generated from databases and biobanks. In case the participant cannot be reached, the researcher should seek advice from the ethics committee for further use of data and samples [18,21,22,26,27,48,58,59].			
Recommendation 14: **Incidental Findings** Researchers should partner with expert health care providers and inform patients and legal guardians about clinically relevant results. Participant's refusal to be informed about clinically relevant results represents an exclusion criterion.	In adults the principle of autonomy and the individual right "to know or not to know" defines the extent to which researchers should inform participants including children and their legal guardians about clinically relevant results detected in research studies. In paediatric studies, the proxy consent does not cover this decision. Here, researchers have a moral duty to inform minor participants and their legal guardians about clinically relevant results that mandate action including research result and incidental findings. Findings should be communicated by an expert clinician [20,22,23,25,27-	I	B	100%

	[29,33,42,43,60].			
Paediatric Data and Biobanks: Operational Principles				
Recommendation 15: Organizational Framework The organizational frameworks for collaborative paediatric data- and biobanks must include a governance structure. Terms of transparency, fair access to data and samples including ownership, authorship of research publications, payment, and reciprocity of sample sharing should be defined. Principles of interoperability should be followed. Data- and /or material transfer agreements should be elaborated and signed between research partners. Researchers should develop a long-term plan for sustainability. Biobanks should be captured in a central electronic tracking system.	An organizational framework prevents ethical and legal conflicts, enables long-term collaborations between participating researchers. The development and endorsement of standards enables higher research interoperability. Transparency of the framework and its policies is necessary for biobanks in all levels. Standardized design and harmonization of data fields enables interoperability between biobanks. A governance structure and a long-term sustainability plan will ensure public trust and long benefits. A central registry for European biobanks will not only reduce the burden of repeated sample collection but also helps to use existing resources in the most efficient way [3,21,26-28,33,37,43,57,61].	I	B	100%
Recommendation 16: Sampling Non-invasive sampling approaches should be preferentially used in children. Standard operating procedures (SOPs) of paediatric sample collection, processing, pre-analytic handling, and shipment should be defined and observed to ensure high quality specimen handling.	The Paediatric Rule mandates minimal invasive sampling, which may result in small quantities of biospecimen and may require designated, harmonized SOPs. Processing of paediatric biospecimen and capture of paediatric data samples should include necessary measures to ensure the accuracy, reliability, quality, and security [20,25,27,28,41,46,57,61,62].	I	B	100%)

Sharing of Data and Samples				
Recommendation 17: Data Harmonization Collaborative databanks should built on available *instruments* of data harmonization, standardized access to data, define measures of high data quality including data dictionaries, and regulate data transfer.	Harmonization of data fosters the interoperability of systems and facilitates the exchange of scientific data. High quality standards enable the possibility of international collaborative research with health related benefits for future generations. Quality assurance measures should be implemented, including conditions to ensure appropriate security and confidentiality during establishment of the collection, storage, use and, where appropriate, transfer of data and materials [3,26-28,30,33,57,61,63].	I	A	100%
Recommendation 18: **Data Protection** Researchers should implement a state-of-the-art data and sample protection system. Secure coding of data and samples should ensure confidentiality while enabling withdrawal of consent, re-consenting, and notification of clinically relevant results. Secure data-sample linkage systems should be established.	Researchers are custodians of personal data and biospecimen. They are responsible for establishing a system of secure safeguards for privacy, confidentiality, and legitimate access. While using anonymous data and samples is the best way to protect personal information, it is not feasible in paediatric research as it limits the researchers' ability to act on withdrawal of consent, the need for re-consenting and the detection, and notification of clinically relevant results. All data handling has to follow the standards of the EU General Data Protection Regulation [20,26,27,30,33,37,46,57,61,63].	I	A	100%
Recommendation 19: Standardization of Transfer Specimen transfer should include standardized packaging and labelling,	Standardization of shipment in accordance with international regulations and laws including all accompanying documents ensures a safe and confidential transfer of biological materials	I	B	100%

accompanying transfer documentation, customs regulations, and sample tracking. The consent form must include the agreement to share data and samples.	across borders. A documented agreement between the sender of the biological materials and the recipient should be signed. The patient's agreement of data and specimen transfer has to be obtained and shared [26-28,35,37].			
Commercialization and Third Party Access				
Recommendation 20: Fees and Incentives Biobanks should enable research to improve medical knowledge. Provision of data and samples should be free; shipment and processing costs should be covered by the requesting research team. Participants or their parents should not receive payment.	Responsible sharing of biospecimen and data should be guided by the principle of the "Universal Declaration of Human Rights, 1948", which grants every individual the right to „share in scientific advancement and its benefits". In fact, the Council of Europe states that sharing of all knowledge and distribution of materials will be obligatory. Collaborative paediatric research aims to maximize discoveries by sharing of resources, data, and samples. Financial incentives should be avoided. The operators of data and biobanks must ensure that any stratified access or fee policies are fair, transparent, and do not inhibit research [20,25,26,28,33,37,39,61,64,65].	I	A	100%
Recommendation 21: Third Parties Researchers have to obtain ethics approval before giving patient data or sample access to third parties. Continuous education of the public about biobanks is important to retain public trust in research.	The autonomy principle mandates that a patient has to give consent to any sharing of data and biospecimen. A researcher therefore should not share any data or specimens with third parties unless the patient permits such submission and an ethics approval was obtained. The most important prerequisite for successful biobank related research is ensuring the public	I	A	100%

	trust. This can be achieved through continuous education of people and protection of privacy [18,20,25,26,30,33,39,43,45].			

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Table 1 Recommendations for collaborative paediatric research including biobanking in Europe

Text of recommendations	Justification	Evidence	Strength	Agree
Guiding Principles				
Recommendation 1: Advancing Care and Discovery Research in children should be supported including international, multi-centre data collection and banking and transfer of biological specimens. Collaboration enables discovery in paediatric diseases and care advancement for children, in particular for those with rare diseases.	Discovery and care advancement in paediatric diseases requires collaborative longitudinal research projects of international scale in order to include sufficient numbers of participants and generate robust scientific data. The international collaborative collection, storage, and sharing of human biological material and associated clinical information reduce the overall burden of sampling for patients and researchers enabling sustained, high-quality research[2,13,14,18,29,31].	I	B	100%
Recommendation 2: Enabling Support Paediatric researchers should be offered research training opportunities, access to mentorship and guidance, protected time, and financial support to conduct paediatric research. Institutional resources for research protocol development, translation services, ethics submission, and research conduct should be made available.	The complexity of collaborative paediatric diseases research and the heterogeneity of rules, regulations, and processes within and across European countries mandate researchers to develop distinct skill sets and content knowledge. Focused, comprehensive training, institutional assistance, and guidance partnered with financial and other support will enable researchers to overcome the disproportionally challenging barriers towards successful multi-national paediatric diseases research requiring sample and data collection [2,16,24,32-34].	I	B	100%
Recommendation 3: Supportive Legislative Framework A supportive legislative framework for international collaborating biobanks is lacking. A framework (WHO, ICH, EMA, FDA, other) should be implemented to overcome legal and ethical barriers in international research. An international binding shipment and custom agreement for biological samples should be established.	The regulatory requirements for paediatric biobanking vary significantly between European countries. This dramatically complicates the implementing of international paediatric diseases biobanks. A unified European framework should be developed and implemented in order to facilitate the international sharing of precious paediatric biospecimen and enable life-saving discoveries [3,20,29,33,35-38].	II	B	100%
Ethics				
Recommendation 4: Centralized Ethics All international collaborative paediatric research should be reviewed by central European Ethics Committees. All auxiliary studies require additional review and approval. The review has to capture all ethical principles including privacy rights.	Designated and highly qualified, independent, and centralized Ethics Committees should serve as Competent Authority for paediatric research. Subsequent, auxiliary studies should be reviewed by the same committee. The resulting single ethics vote captures the highest ethical principles and privacy standards. Subsequently National Ethics Committee reviews are solely tasked with evaluating cultural appropriateness [16,17,19,21-23,29,37,39].	I	B	94%

Recommendation 5: Standardization and Transparency All collaborative paediatric research applications in the European Community should be filed in a standardized format and be submitted to a central electronic application portal. Following submission the review process should be transparent and electronically traceable.	The current necessity of multiple ethics applications, the large variability in the submitting formats, and the lack of transparency of the reviewing process hinder collaborative paediatric research within the EU. A standardized submission and approval process through a central application portal as implemented in the EU portal for all clinical trials will overcome this barrier and facilitate research and care advancement [17].	I	B	100%
Recommendation 6: Central Competency The European Central Ethics Application Board should rapidly assess all multicentre applications for meeting formal EU-standards. All applications including timelines should be tracked in a central repository. The application should be transferred to the applicant's designated National Ethics Committee for Paediatric Research and Biobanking and undergo review including compliance with the specific ethical principles. After sign off, the other participating National Ethics Committees should rapidly adopt the decision.	The standardization of application requirements and a unified primary, central review process overcomes barriers by simplifying the process while increasing the quality in accordance to the European regulation on clinical trials on medicinal products for human use (Clinical Trials Regulation)[17,40].	I	B	100%
Recommendation 7(1): Membership expertise Each National Ethics Committee for Paediatric Research and Biobanking should operate according to uniform standards. Membership: Each Committee has to include independent experts in paediatric research, lay members (non-professionals including patient / parent organizations or community advocates) and those with specific content expertise including genetics to review specific applications when appropriate.	The ethics committee review of collaborative paediatric research studies and biobanking requires specific expertise reflected in its membership: Paediatricians should provide advice on clinical, ethical, and psychosocial aspects of research in minors. Lay members should offer support evaluating individual and societal impact of the proposed research. The review of genetic studies mandates an additional content expert for guidance[16,17,21,40-42].	I	A	94%
Recommendation 7(2): Support and Clarity Ethics application: Each Committee should provide direct assistance, clear instructions, and training courses to support the researcher. Instructions and applications should be written in a simple, universally understood language. Fees: Administrative fees should exclusively be charged in non-academic research; if charged, they should not constitute an obstacle.	Administrative support, training opportunities, and transparent, simple instructions will help facilitate the paediatric research ethics application. For investigator initiated, non-commercial studies fees should not constitute a barrier to research. Fees should be set solely on the basis of cost recovery principles and be reduced or waived when appropriate [16,17,24,43].	I	A	100%
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Recommendation 9: Paediatric Rule Children should receive special protection when included in data and biobank studies.	Children are a vulnerable population. The potential risks including privacy risks related to genetic information, physical and emotional harms, and disrespect of values should be minimized during sample collection and the duration of the research study. Justification is required when inviting vulnerable individuals to serve as research subjects, the risk should be minimal and the means of protecting rights and welfare must be strictly applied [16,18,19,21,23,29,38,39,41,44].	I	A	100%
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Recommendation 10: Integration of Minors Voluntary and age-appropriate informed consent/assent has to be obtained from legal guardians and/or minors as appropriate according to the international guidelines (ICH, WHO, others) before paediatric data and biospecimen can be collected and used for research. Minors should be integrated into the process of consent and those capable of forming an opinion and assessing the information given, should be asked to give assent or consent, as appropriate.	Children have the right to be included in research and benefit from research discoveries. All research mandates voluntary, informed consent given by a competent individual, who has received the necessary information and has adequately understood the information. The decision to participate has to be reached without coercion, undue influence or intimidation. Informed consent embodies the individual's freedom of choice and respects the individual's autonomy. Legal guardians may serve as proxies for minors, who do not have full capacity, in the consent process; children should be integrated in the consent process and their opinion and views have to be respected [8,16,18,19,21-23,27,29,39,42,45-49].	I	A	100%
Recommendation 11: Enabling Informed Consent All information given to the child and the legal guardian should be age appropriate, written, and presented by a competent person in the country's official language. Paediatric participants and legal guardians should be granted appropriate time to make and reconsider their decision. Withdrawal of consent should be possible at any time of the study.	The process of consenting must not be simply a ritual recitation of the contents of a written document. The information must be conveyed in language that suits the individual's level of understanding. Parents/legal guardians and children must be given time and opportunity for discussion to make the decision without any pressure to consent. Participants should be informed that consent/assent can be withdrawn at any time. Exercising the right to withdraw cannot entail consequences in medical care services [16,18,19,21-23,39,42,44,45,48,50].	I	B	100%
Recommendation 12: Scope of Consent The scope of consent should preferably be broad. Broad consent should include future research opportunities, possibility to share samples and data with national and/or international research partners. Broad consent should include the possibility to re-contact participants. Consent forms need to be internationally harmonized to ensure international research	Broad consent reduces the burden for participants as it avoids the need for re-sampling of biospecimen and re-collection of data in addition to the need for re-consenting. Broad consent avoids the need to re-contact and re-consent participants, which may represent a significant barrier to conducting research. It allows for novel research to be conducted that had not been conceptualized at the time of the initial study. Permission for data and specimen transfer should be included in the harmonized consent	I	B	100%

projects. Consent forms have to include the possibility for specimen shipment and data transfer. Consenting should include the opportunity to opt out of certain aspects of research.	forms. A governance specification and an opt-out option have to be included enabling participants to limit the use of their specimens and data to distinct research questions [18,22,23,26,33,39,41,44,51-53].			
Recommendation 13: Re-consenting Paediatric participants that have previously only given assent should be re-contacted for consent to an ongoing study when reaching legal age. Researchers should make considerable effort to re-contact participants for further use of data and samples. The ethics committee should evaluate the option of further use of data and sample, if participants are not reachable.	At time of reaching legal age the formal legal status of the participant changes. This mandates obtaining re-consent since the initial consent was not obtained from the minor and therefore has limited temporal scope. Allowing the competent child a right to withdraw materials given into the biobank by proxy consent is consistent with the idea of a child's "right to an open future", which states that choices made for a child when being a minor should not preclude the right to make decisions when reaching legal age. The former minor has now full autonomy and is now able to oversee the dimension of the research and can give informed consent for ongoing research generated from databases and biobanks. In case the participant cannot be reached, the researcher should seek advice from the ethics committee for further use of data and samples [14,17,18,22,23,44,54,55].	I	A	88%
Recommendation 14: **Incidental Findings** Researchers should partner with expert health care providers and inform patients and legal guardians about clinically relevant results. Participant's refusal to be informed about clinically relevant results represents an exclusion criterion.	In adults the principle of autonomy and the individual right "to know or not to know" defines the extent to which researchers should inform participants including children and their legal guardians about clinically relevant results detected in research studies. In paediatric studies, the proxy consent does not cover this decision. Here, researchers have a moral duty to inform minor participants and their legal guardians about clinically relevant results that mandate action including research result and incidental findings. Findings should be communicated by an expert clinician [16,18,19,21,23-25,29,38,39,56].	I	B	100%
Paediatric Data and Biobanks: Operational Principles				
Recommendation 15: Organizational Framework The organizational frameworks for collaborative paediatric data- and biobanks must include a governance structure. Terms of transparency, fair access to data and samples including ownership, authorship of research publications, payment, and reciprocity of sample sharing should be defined. Principles of interoperability should be followed. Data- and /or material transfer agreements should be elaborated and signed between research partners. Researchers should develop a long-term plan for sustainability. Biobanks should be captured in a central electronic tracking system.	An organizational framework prevents ethical and legal conflicts, enables long-term collaborations between participating researchers. The development and endorsement of standards enables higher research interoperability. Transparency of the framework and its policies is necessary for biobanks in all levels. Standardized design and harmonization of data fields enables interoperability between biobanks. A governance structure and a long-term sustainability plan will ensure public trust and long benefits. A central registry for European biobanks will not only reduce the burden of repeated sample collection but also helps to use existing resources in the most efficient way [3,17,22-24,29,33,39,53,57].	I	B	100%

Recommendation 16: Sampling Non-invasive sampling approaches should be preferentially used in children. Standard operating procedures (SOPs) of paediatric sample collection, processing, pre-analytic handling, and shipment should be defined and observed to ensure high quality specimen handling.	The Paediatric Rule mandates minimal invasive sampling, which may result in small quantities of biospecimen and may require designated, harmonized SOPs. Processing of paediatric biospecimen and capture of paediatric data samples should include necessary measures to ensure the accuracy, reliability, quality, and security [16,21,23,24,37,42,53,57,58].	I	B	100%)
Sharing of Data and Samples				
Recommendation 17: Data Harmonization Collaborative databanks should built on available *instruments* of data harmonization, standardized access to data, define measures of high data quality including data dictionaries, and regulate data transfer.	Harmonization of data fosters the interoperability of systems and facilitates the exchange of scientific data. High quality standards enable the possibility of international collaborative research with health related benefits for future generations. Quality assurance measures should be implemented, including conditions to ensure appropriate security and confidentiality during establishment of the collection, storage, use and, where appropriate, transfer of data and materials [3,22-24,26,29,53,57,59].	I	A	100%
Recommendation 18: **Data Protection** Researchers should implement a state-of-the-art data and sample protection system. Secure coding of data and samples should ensure confidentiality while enabling withdrawal of consent, re-consenting, and notification of clinically relevant results. Secure data-sample linkage systems should be established.	Researchers are custodians of personal data and biospecimen. They are responsible for establishing a system of secure safeguards for privacy, confidentiality, and legitimate access. While using anonymous data and samples is the best way to protect personal information, it is not feasible in paediatric research as it limits the researchers' ability to act on withdrawal of consent, the need for re-consenting and the detection, and notification of clinically relevant results. All data handling has to follow the standards of the EU General Data Protection Regulation [16,22,23,26,29,33,42,53,57,59].	I	A	100%
Recommendation 19: Standardization of Transfer Specimen transfer should include standardized packaging and labelling, accompanying transfer documentation, customs regulations, and sample tracking. The consent form must include the agreement to share data and samples.	Standardization of shipment in accordance with international regulations and laws including all accompanying documents ensures a safe and confidential transfer of biological materials across borders. A documented agreement between the sender of the biological materials and the recipient should be signed. The patient's agreement of data and specimen transfer has to be obtained and shared [22-24,31,33].	I	B	100%
Commercialization and Third Party Access				
Recommendation 20: Fees and Incentives Biobanks should enable research to improve medical knowledge. Provision of data and samples should be free; shipment and processing costs should be covered by the requesting research team. Participants or their parents should not receive payment.	Responsible sharing of biospecimen and data should be guided by the principle of the "Universal Declaration of Human Rights, 1948", which grants every individual the right to „share in scientific advancement and its benefits". In fact, the Council of Europe states that sharing of all knowledge and distribution of materials will be obligatory. Collaborative paediatric research aims to maximize discoveries by sharing of resources, data, and samples. Financial incentives should be avoided. The operators of data and biobanks must ensure that any stratified access or fee policies are fair,	I	A	100%

	transparent, and do not inhibit research [16,21,22,24,29,33,35,57,60,61].			
Recommendation 21: Third Parties Researchers have to obtain ethics approval before giving patient data or sample access to third parties. Continuous education of the public about biobanks is important to retain public trust in research.	The autonomy principle mandates that a patient has to give consent to any sharing of data and biospecimen. A researcher therefore should not share any data or specimens with third parties unless the patient permits such submission and an ethics approval was obtained. The most important prerequisite for successful biobank related research is ensuring the public trust. This can be achieved through continuous education of people and protection of privacy [14,16,21,22,26,29,35,39,41].	I	A	100%

Option 2 (for space constrains purposes)

Table 1 Recommendations for collaborative paediatric research including biobanking in Europe

Text of recommendations	Justification	Evidence	Strength	Agree
Guiding Principles				
Recommendation 1: Advancing Care and Discovery	2,13,14,18,29,31	I	B	100%
Recommendation 2: Enabling Support	2,16,24,32-34	I	B	100%
Recommendation 3: Supportive Legislative Framework	3,20,29,33,35-38	II	B	100%
Ethics				
Recommendation 4: Centralized Ethics	16,17,19,21-23,29,37,39	I	B	94%
Recommendation 5: Standardization and Transparency	17	I	B	100%
Recommendation 6: Central Competency	17,40	I	B	100%
Recommendation 7(1): Membership expertise	16,17,21,40-42	I	A	94%
Recommendation 7(2): Support and Clarity	16,17,24,43	I	A	100%
Paediatric Principles				
Recommendation 8: Subsidiarity	16,18,19,21,23,29,37,38,40	I	A	88%
Recommendation 9: Paediatric Rule	16,18,19,21,23,29,38,39,41,44	I	A	100%

Consent in Paediatric Research				
Recommendation 10: Integration of Minors	8,16,18,19,21-23,27,29,39,42,45-49	I	A	100%
Recommendation 11: Enabling Informed Consent	16,18,19,21-23,39,42,44,45,48,50	I	B	100%
Recommendation 12: Scope of Consent	18,22,23,26,33,39,41,44,51-53	I	B	100%
Recommendation 13: Re-consenting	14,17,18,22,23,44,54,55	I	A	88%
Recommendation 14: Incidental Findings	16,18,19,21,23-25,29,38,39,56	I	B	100%
Paediatric Data and Biobanks: Operational Principles				
Recommendation 15: Organizational Framework	3,17,22-24,29,33,39,53,57	I	B	100%
Recommendation 16: Sampling	16,21,23,24,37,42,53,57,58	I	B	100%)
Sharing of Data and Samples				
Recommendation 17: Data Harmonization	3,22-24,26,29,53,57,59	I	A	100%
Recommendation 18: Data Protection	16,22,23,26,29,33,42,53,57,59	I	A	100%
Recommendation 19: Standardization of Transfer	22-24,31,33	I	B	100%
Commercialization and Third Party Access				
Recommendation 20: Fees and Incentives	16,21,22,24,29,33,35,57,60,61	I	A	100%
Recommendation 21: Third Parties	14,16,21,22,26,29,35,39,41	I	A	100%

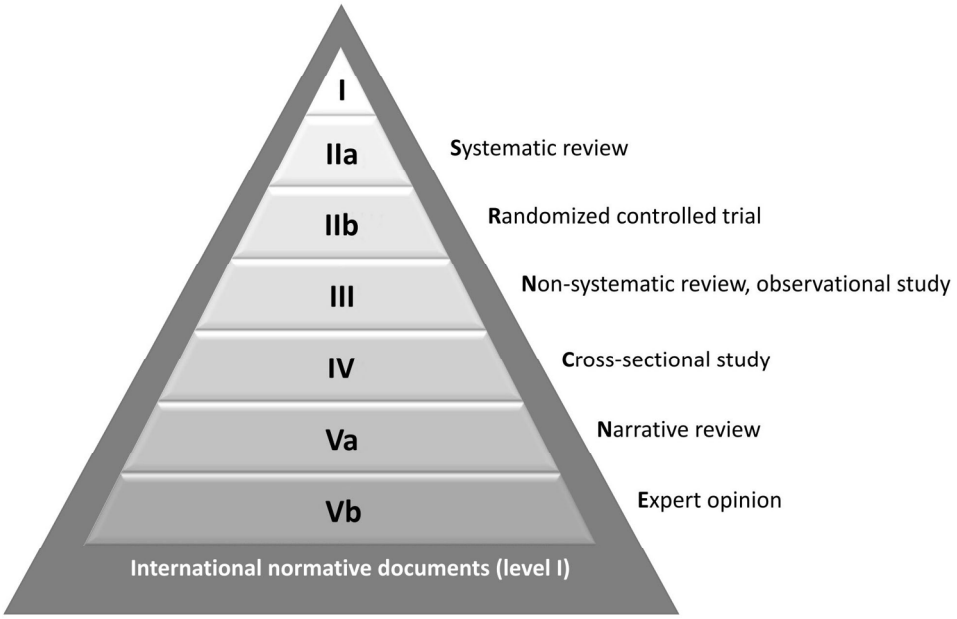

Figure 1
Modified hierarchy of evidence pyramid for inclusion of normative documents
Legend: The pyramid depicting the hierarchy of evidence was modified with guidance of the Cochrane collaboration to enable the inclusion of all available scientific evidence and international normative documents in the systematic review.

173x114mm (300 x 300 DPI)

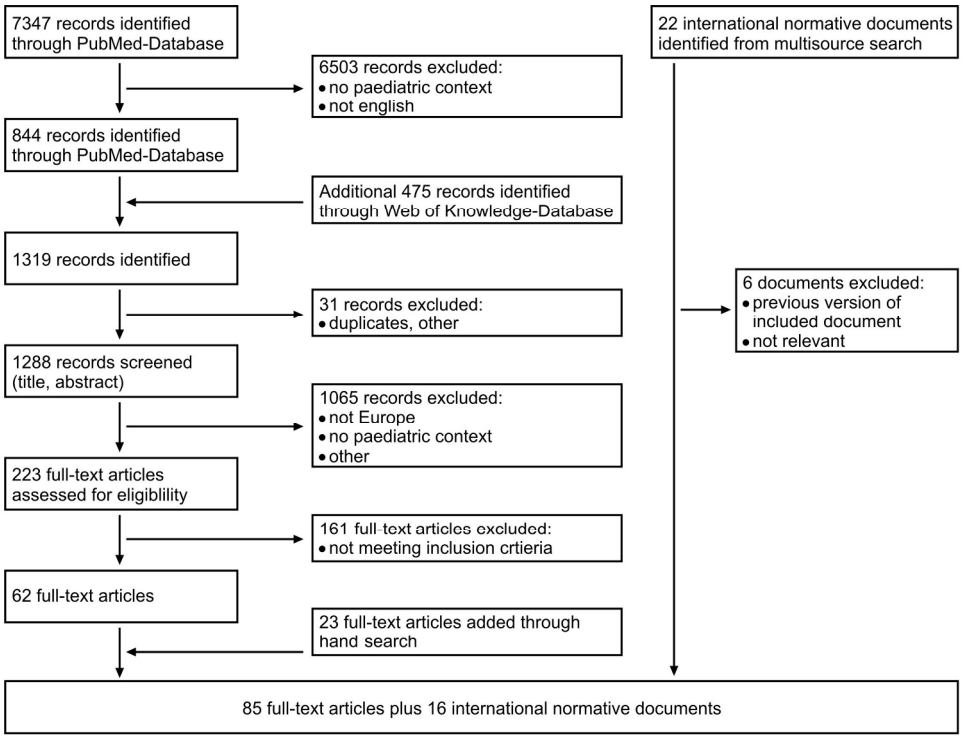

Figure 2
Literature selection flow chart
Legend: The search included the following MESH-terms: data collection, ethics, biological specimen banks, confidentiality, informed consent by minors, specimen handling, quality improvement, and jurisprudence. In addition, the following subheadings were used: legislation, classification, methods, organization, administration, standards, and instrumentation. The search was limited to literature relevant to the paediatric age group (0 to 18 years of age) and to Europe.

Search strategy

((((((("Data Collection/ethics"[Mesh] OR "Data Collection/legislation and jurisprudence"[Mesh]))) OR ((((((
"Ethics/classification"[Mesh] OR "Ethics/ethics"[Mesh] OR "Ethics/legislation and jurisprudence"[Mesh] OR
"Ethics/methods"[Mesh] OR "Ethics/organization and administration"[Mesh] OR "Ethics/standards"[Mesh])))
OR ethics)) AND (("Biological Specimen Banks/classification"[Mesh] OR "Biological Specimen
Banks/ethics"[Mesh] OR "Biological Specimen Banks/instrumentation"[Mesh] OR "Biological Specimen
Banks/legislation and jurisprudence"[Mesh] OR "Biological Specimen Banks/methods"[Mesh] OR "Biological
Specimen Banks/organization and administration"[Mesh] OR "Biological Specimen Banks/standards"[Mesh]
)))) OR (((("Confidentiality/ethics"[Mesh] OR "Confidentiality/legislation and jurisprudence"[Mesh] OR
"Confidentiality/organization and administration"[Mesh] OR "Confidentiality/standards"[Mesh]))) AND ((
"Biological Specimen Banks/classification"[Mesh] OR "Biological Specimen Banks/ethics"[Mesh] OR
"Biological Specimen Banks/instrumentation"[Mesh] OR "Biological Specimen Banks/legislation and
jurisprudence"[Mesh] OR "Biological Specimen Banks/methods"[Mesh] OR "Biological Specimen
Banks/organization and administration"[Mesh] OR "Biological Specimen Banks/standards"[Mesh])))) OR ((
"Informed Consent By Minors/ethics"[Mesh] OR "Informed Consent By Minors/legislation and
jurisprudence"[Mesh] OR "Informed Consent By Minors/organization and administration"[Mesh] OR
"Informed Consent By Minors/standards"[Mesh]))) OR (((((("Specimen Handling/ethics"[Mesh] OR
"Specimen Handling/legislation and jurisprudence"[Mesh]))) OR (("Specimen Handling/standards"[Majr])
AND "Quality Improvement"[Mesh])) OR (("Specimen Handling"[Mesh]) AND "Ethics"[Mesh])) OR
(("Jurisprudence"[Majr]) AND "Specimen Handling"[Majr])) OR ((((("Specimen Handling"[Majr]) And
("legislation and jurisprudence" [Subheading]))) OR (("Specimen Handling"[Majr]) AND "ethics"
[Subheading])))))) OR (("Data Collection/ethics"[Majr:NoExp] OR "Data Collection/legislation and

jurisprudence"[Majr:NoExp]))

199x150mm (300 x 300 DPI)

Table S1

Study characteristics of the 85 included publications

Author	Year	Title	Journal	Study design	Evidence level	Nationality of first author
J. Allen, P. McCarthy, E. M. Dempsey and J. O. Hourihane	2013	Irish public would prefer legislation to protect Guthrie card archive rather than destroy it	BMJ	cross sectional study	IV	Ireland
V. Anastasova, A. Mahalatchimy, E. Rial-Sebbag, J. M. Anto Boque, T. Keil, J. Sunyer, J. Bousquet and A. Cambon-Thomsen	2013	Communication of results and disclosure of incidental findings in longitudinal paediatric research	Pediatric Allergy and Immunology	non-systematic review	III	France
Ashcroft R.E., Goodenough T., Willamson E., Kent J.	2003	Children´s consent to research participation: social context and personal experience invalidate fixed cutoff rules	The American Journal of Bioethics	expert opinion	V b	UK
J. Balaguer, A. Canete, E. Costa, S. Oltra, M. Hernandez and V. Castel	2006	Tumour banks in pediatric oncology	Clin Transl Oncol	cross sectional	IV	Spain
K. Birmingham and A. Doyle	2009	Ethics and governance of a longitudinal birth cohort	Paediatr Perinat Epidemiol	non-systematic review	III	UK
D. Budimir, O. Polasek, A. Marusic, I. Kolcic, T. Zemunik, V. Boraska, A. Jeroncic, M. Boban, H. Campbell and I. Rudan	2011	Ethical aspects of human biobanks: a systematic review	Croat Med J	systematic review	II a	Croatia
A. Cambon-Thomsen, E. Rial-Sebbag and B. M. Knoppers	2007	Trends in ethical and legal frameworks for the use of human biobanks	Eur Respir J	non-systematic review	III	France
P. Chatzipantazi, K. M. Roy, S. O. Cameron, D. Goldberg, R. Welbury and J. Bagg	2004	The feasibility and acceptability of collecting oral fluid from healthy children for anti-HCV testing	Arch Dis Child	cross sectional	IV	UK

D. Deplanque, G. Birraux, P.-H. Bertoye, E. Postaire, N. Round Table and X. Giens	2009	Collections of Human Biological Samples for Scientific Purposes. Why do Current Regulation Need to be Clarified and How?	Therapie	expert opinion	V b	France
C. M. Douglas, C. G. van El, A. Faulkner and M. C. Cornel	2012	Governing biological material at the intersection of care and research: the use of dried blood spots for biobanking	Croat Med J	expert opinion	V b	Netherlands
I. Ellis, G. Mannion and A. Warren-Jones	2003	Retained human tissues: a molecular genetics goldmine or modern grave robbing? A legal approach to obtaining and using stored human samples	Med Law	expert opinion	V b	UK
S. Eriksson, A. T. Höglund and G. Helgesson	2008	Do Ethical Guidelines Give Guidance?A Critical Examination of Eight Ethics Regulations	Cambridge Quarterly of Healthcare Ethics	cross sectional study	IV	
I. Garcia-Merino, N. de las Cuevas, J. Luis Jimenez, A. Garcia, J. Gallego, C. Gomez, D. Garcia, M. Angeles Munoz-Fernandez and H. I. V. B. Spanish	2010	Pediatric HIV BioBank: A New Role of the Spanish HIV BioBank in Pediatric HIV Research	AIDS Res Hum Retroviruses	cross-sectional study	IV	Spain
N. A. A. Giesbertz, A. L. Bredenoord and J. J. M. van Delden	2014	Clarifying assent in pediatric research	European journal of human genetics : EJHG	narrative literature review	V a	Netherlands
E. Gluckman	2000	Ethical and legal aspects of placental/cord blood banking and transplant	Haematologica	expert opinion	V b	France
B. Godard, J. Schmidtke, J.-J. Cassiman and S. Ayme	2003	Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective	European Journal of Human Genetics	non-systematic review	III	France
T. Goodenough, E. Williamson, J. Kent and R. Ashcroft	2004	Ethical protection in research: including children in the debate	Researchers and their "subjects"	cross-sectional study	IV	UK
T. Goodenough, E. Williamson, J. Kent and R. Ashcroft	2011	'What Did You Think About That?' Researching Children's Perceptions of Participation in a Longitudinal Genetic Epidemiological Study	Children and Society	non-systematic literature review	III	UK

M. G. Hansson	2009	Ethics and biobanks	British Journal of Cancer	non-systematic review	III	Sweden
M. G. Hansson	2005	Building on relationships of trust in biobank research	J Med Ethics	Expert Opinion	V b	Sweden
M. G. Hansson	2007	For the safety and benefit of current and future patients	Pathobiology	Expert Opinion	V b	Sweden
S. O. Hansson	2004	The ethics of biobanks	Cambridge Quarterly of Healthcare Ethics	Expert opinion	V b	Sweden
G. Helgesson and U. Swartling	2008	Views on data use, confidentiality and consent in a predictive screening involving children	J Med Ethics	cross sectional	IV	Sweden
G. Helgesson	2005	Children, longitudinal studies, and informed consent	Medicine, Health Care and Philosophy	narrative literature review	V a	Sweden
G. Helgesson, M. G. Hansson, J. Ludvigsson and U. Swartling	2010	What parents find important when participating in longitudinal studies: results from a questionnaire	Clinical Ethics	cross sectional study	IV	
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2009	Biological sample collections from minors for genetic research: a systematic review of guidelines and position papers	Eur J Hum Genet	systematic review	II a	Belgium
K. Hens, H. Nys, J.-J. Cassiman and K. Dierickx	2009	Genetic Research on Stored Tissue Samples From Minors: A Systematic Review of the Ethical Literature	Am J Med Genet A	systematic review	II a	Belgium
K. Hens, J. J. Cassiman, H. Nys and K. Dierickx	2011	Children, biobanks and the scope of parental consent	Eur J Hum Genet	non-systematic review	III	Belgium
K. Hens, E. Levesque and K. Dierickx	2011	Children and biobanks: a review of the ethical and legal discussion	Hum Genet	non-systematic review	III	Belgium

K. Hens, C. E. Van El, P. Borry, A. Cambon-Thomsen, M. C. Cornel, F. Forzano, A. Lucassen, C. Patch, L. Tranebjaerg, E. Vermeulen, E. Salvaterra, A. Tibben and K. Dierickx	2013	Developing a policy for paediatric biobanks: principles for good practice	Eur J Hum Genet	non-systematic review	III	Belgium
K. Hens and K. Dierickx	2010	Human tissue samples for research. A focus group study in adults and teenagers in Flanders	Genet Couns	cross-sectional study	IV	Belgium
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2011	The storage and use of biological tissue samples from minors for research: a focus group study	Public Health Genomics	cross-sectional study	IV	Belgium
K. Hens, J. Snoeck, H. Nys, J. J. Cassiman and K. Dierickx	2010	An exploratory survey of professionals on the use of stored tissue samples from minors for genetic research	Genetics and Molecular Research	cross-sectional study	IV	Belgium
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2011	Risks, Benefits, Solidarity: A Framework for the Participation of Children in Genetic Biobank Research	Journal of Pediatrics	narrative literature review	V a	Belgium
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2011	The return of individual research findings in paediatric genetic research	J Med Ethics	narrative literature review	V a	Belgium
K. Hens, J. Wright and K. Dierickx	2009	Biobanks: oversight offers protection	Science	Letter to the editor	V b	Belgium
B. Hofmann	2009	Broadening consent-and diluting ethics?	J Med Ethics	narrative literature review	V a	Norway
S. Holm	2005	Informed Consent and the Bio-banking of Material from Children	Genomics, society and politics	expert opinion	V b	UK
C. Jackson, M. Dixon-Woods, M. Tobin, B. Young, D. Heney and K. Pritchard-Jones	2009	Seeking consent to tissue banking: a survey of health professionals in childhood cancer	Eur J Cancer Care (Engl)	cross sectional	IV	UK

V. W. V. Jaddoe, R. Bakker, C. M. van Duijn, A. J. van der Heijden, J. Lindemans, J. P. Mackenbach, H. A. Moll, E. A. P. Steegers, H. Tiemeier, A. G. Uitterlinden, F. C. Verhulst and A. Hofman	2007	The Generation R Study Biobank: a resource for epidemiological studies in children and their parents	European Journal of Epidemiology	Observational Study	III	Netherlands
S. Kirk	2007	Methodological and ethical issues in conducting qualitative research with children and young people: a literature review	Int J Nurs Stud	non-systematic review	III	UK
M. F. Laker	2006	The Human Tissue Act: implications for clinical biochemistry	Ann Clin Biochem	expert opinion	V b	UK
V. Lambert and M. Glacken	2011	Engaging with children in research: Theoretical and practical implications of negotiating informed consent/assent	Nurs Ethics	non-systematic review	III	Ireland
H. Lochmuller and P. Schneiderat	2010	Biobanking in Rare Disorders	Rare Diseases Epidemiology	expert opinion	V b	UK
N. Martin, P. Krol, S. Smith, K. Murray, C. A. Pilkington, J. E. Davidson, L. R. Wedderburn and G. Juvenile Dermatomyositis Res	2011	A national registry for juvenile dermatomyositis and other paediatric idiopathic inflammatory myopathies: 10 years' experience; the Juvenile Dermatomyositis National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies	Rheumatology	cross-sectional study	IV	UK
D. Mascalzoni, A. C. J. W. Janssens, A. Stewart, P. Pramstaller, U. Gyllensten, I. Rudan, C. M. van Duijn, J. F. Wilson, H. Campbell, R. Mc Quillan and E. Consortium	2010	Comparison of participant information and informed consent forms of five European studies in genetic isolated populations	European Journal of Human Genetics	expert opinion	V b	Italy
J. V. McHale	2011	Accountability, Governance and Biobanks: The Ethics and Governance Committee as Guardian or as Toothless Tiger?	Health Care Anal	narrative literature review	V a	UK
J. McHale, M. Habiba, M. Dixon-Woods, D. Cavers, D. Heney and K. Pritchard-Jones	2007	Consent for childhood cancer tissue banking in the UK: the effect of the Human Tissue Act 2004	Lancet Oncol	narrative literature review	V a	UK

D. F. Merlo, L. E. Knudsen, K. Matusiewicz, L. Niebroj and K. H. Vahakangas	2007	Ethics in studies on children and environmental health	J Med Ethics	narrative literature review	V a	Italy
D. F. Merlo, K. Vahakangas and L. E. Knudsen	2008	Scientific integrity: critical issues in environmental health research.	Environmental Health	narrative literature review	V a	Italy
S. E. Mumford	1999	Children of the 90s II: challenges for the ethics and law committee	Arch Dis Child Fetal Neonatal Ed	expert opinion	V b	UK
S. E. Mumford	1999	Children of the 90s: ethical guidance for a longitudinal study	Arch Dis Child Fetal Neonatal Ed	expert opinion	V b	UK
B. Norgaard-Pedersen and D. M. Hougaard	2007	Storage policies and use of the Danish Newborn Screening Biobank	J Inherit Metab Dis	expert opinion	V a	Denmark
B. Norgaard-Pedersen and H. Simonsen	1999	Biological specimen banks in neonatal screening	Acta Paediatr Suppl	expert opinion	V a	Denmark
J. Pawlikowski, J. Sak and K. Marczewski	2011	Biobank research and ethics: the problem of informed consent in Polish biobanks	Archives of Medical Science	cross-sectional study	IV	Poland
C. Petrini and M. Farisco	2011	Informed consent for cord blood donation. A theoretical and empirical study	Blood Transfus	cross-sectional study	IV	Italy
C. Petrini, L. Lombardini, S. Pupella, A. N. Costa and G. Grazzini	2011	Collection, Storage, and Allogeneic Use of Cord Blood: Informed Consent Form Used by the Italian Biobank Network	Biopreservation and biobanking	expert opinion	IV	Italy
C. Petrini, A. Olivieri, C. Corbetta, R. Cerone, G. D'Agnolo and A. Bompiani	2012	Common criteria among States for storage and use of dried blood spot specimens after newborn screening	Ann Ist Super Sanita	expert opinion	V a	Italy
C. Petrini	2012	Ethical and legal considerations regarding the ownership and commercial use of human biological materials and their derivatives	Journal of Blood Medicine	narrative literature review	V a	Italy

W. Pinxten and K. Dierickx	2008	The Implementation of Directive 2001/20/EC into Belgian Law and the Specific Provisions on Pediatric Research	European Journal of Health Law 15 (2008) 153-161	expert opinion	V b	Belgium
W. Pinxten, K. Dierickx and H. Nys	2009	Ethical principles and legal requirement for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials	Eur J Pediatr	expert opinion	V b	Belgium
O. Polasek	2013	Future of biobanks - bigger, longer, and more dimensional	Croat Med J	narrative literature review	V a	Croatia
M. M. Reid	1994	Research on leukaemia cells surplus to diagnostic needs in children	J Med Ethics	expert opinion	V b	UK
K. Rushforth and P. A. McKinney	2005	Issues of patient consent: a study of paediatric high-dependency care	Br J Nurs	narrative literature review	V a	UK
E. Salvaterra, F. Locatelli, S. Strazzer, R. Borgatti, G. D'Angelo and L. Lenzi	2014	Paediatric Biobanks: Opinions, Feelings and Attitudes of Parents towards the Specimen Donation of Their Sick Children to a Hypothetical Biobank	Pathobiology	cross-sectional study	IV	Italy
E. Salvaterra, R. Giorda, M. T. Bassi, R. Borgatti, L. E. Knudsen, A. Martinuzzi, M. Nobile, U. Pozzoli, G. P. Ramelli, G. L. Reni, D. Rivolta, M. A. Stazi, S. Strazzer, C. Thijs, V. Toccaceli, A. Trabacca, A. C. Turconi, S. Zanini, C. Zucca, N. Bresolin and L. Lenzi	2012	Pediatric Biobanking: A Pilot Qualitative Survey of Practices, Rules, and Researcher Opinions in Ten European Countries	Biopreservation and Biobanking	cross-sectional study	IV	Italy
N. J. Sebire and M. Dixon-Woods	2007	Towards a new era of tissue-based diagnosis and research	Chronic Illness	narrative literature review	V a	UK
C. Soto, C. Tarrant, K. Pritchard-Jones and M. Dixon-Woods	2012	Consent to tissue banking for research: qualitative study and recommendations	Arch Dis Child	cross-sectional study	IV	UK

S. Sterckx and K. Van Assche	2011	The New Belgian Law on Biobanks: Some Comments from an Ethical Perspective	Health Care Anal	expert opinon	V b	Belgium
U. G. Stolt, P. E. Liss, T. Svensson and J. Ludvigsson	2002	Attitudes to bioethical issues: a case study of a screening project	Social Science and Medicine	cross-sectional study	IV	Sweden
U. G. Stolt, G. Helgesson, P. E. Liss, T. Svensson and J. Ludvigsson	2005	Information and informed consent in a longitudinal screening involving children: a questionnaire survey	European Journal of Human Genetics	cross sectional study	IV	
L. Stultiëns, T. Goffin, P. Borry, K. Dierickx and H. Nys	2007	Minors and informed consent: a comparative approach.	Eur J Health Law	non-systematic review	III	Belgium
U. Swartling, G. Helgesson, M. G. Hansson and J. Ludvigsson	2008	Parental authority, research interests and children's right to decide in medical research – an uneasy tension?	Clinical Ethics	cross sectional study	IV	
U. Swartling, G. Helgesson, M. G. Hansson and J. Ludvigsson	2009	Split views among parents regarding children's right to decide about participation in research: a questionnaire survey	Research ethics	cross sectional study	IV	
L. Taylor, D. Casson and M. J. Platt	2003	Issues and experience around the Paediatric Register of Inflammatory Bowel Disease	Arch Dis Child	expert opinion	V b	UK
V. Toccaceli, L. Serino and M. A. Stazi	2014	Informed consent, and an ethico- legal framework for paediatric observational research and biobanking: the experience of an Italian birth cohort study	Cell and Tissue Banking	non-systematic review	III	Italy
P. Tozzo, R. Pegoraro and L. Caenazzo	2010	Biobanks for non-clinical purposes and the new law on forensic biobanks: does the Italian context protect the rights of minors?	J Med Ethics	Expert opinion	Vb	Italy
A. Martin Uranga, M. C. Martin Arribas, C. Jaeger and M. Posadas	2005	Outstanding ethical-legal issues on biobanks. An overview on the regulations of the Member States of the Eurobiobank project	Book chapter	expert opinion	V b	Spain
K. Vahakangas	2013	Research ethics in the post-genomic era	Environmental and MolecularMutagenesis	non-systematic review	III	Finland

S. van der Pal, B. Sozanska, D. Madden, A. Kosmeda, A. Debinska, H. Danielewicz, A. Boznanski and S. Detmar	2011	Opinions of Children about Participation in Medical Genetic Research	Puplic Health Genomics	cross-sectional study	IV	Netherlands
M. Waligora, V. Dranseika and J. Piasecki	2014	Child's assent in research: age threshold or personalisation?	BMC Med Ethics	expert opinion	V b	Poland
A. E. Westra, J. M. Wit, R. N. Sukhai and I. D. de Beaufort	2011	Regulating "higher risk, no direct benefit" studies in minors	The American Journal of Bioethics	expert opinion	V b	Netherlands
R. Wheeler	2012	Competent for confidence at 12 years of age?	Arch Dis Child	expert opinion	V b	UK
G. Williams	2012	Children as means and ends in large-scale medical research	bioethics	Expert opinion	Vb	Eb
E. Williamson	2005	Conducting research with children: The limits of confidentiality and child protection protocols	Children and Society	expert opinion	V b	UK

Table S2

Characteristics of the included 16 normative documents

Title	Evidence	Type of normative document
United Nations (UN) Universal Declaration of Human Rights, 1948	I	International declaration
United Nations (UN) Convention on the rights of the child 1989 (based on Declaration of the Rights of the Child)	I	International declaration
World Medical Association (WMA) Declaration of Helsinki Last version 2013	I	International declaration
United Nations Educational, Scientific and Cultural Organization (UNESCO) 2003 International Bioethics Committee (IBC) International declaration on human genetic data	I	International guideline regarding biomedical research and biobanks
World Health Organization (WHO) 2003 Genetic databases. Assessing the benefits and the impact on human and patient rights	I	International guideline regarding biomedical research and biobanks
Organization of Economic Co-operation and Development (OECD) 2009 Recommendation on Human Bioanks and Genetic Research Databases	I	International guideline regarding biomedical research and biobanks

Council for International Organizations of Medical Science (CIOMS) 2008 International Ethical Guidelines on Epidemiological Studies	I	International guideline regarding biomedical research and biobanks
Council for International Organizations of Medical Science (CIOMS)2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects	I	International guideline regarding biomedical research and biobanks
REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	I	European legislation
Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)	I	European legislation
Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin (Adopted by the Committee of Ministers on 11 May 2016 at the 1256th meeting of the Ministers' Deputies)	I	European recommendation
Data storage and DNA banking for biomedical research: technical, social and ethical issues Recommendations of the European Society of Human Genetics European Journal of Human Genetics (2003) 11, Suppl 2, S8 –S10. doi:10.1038/sj.ejhg.5201115	I	European recommendation
COUNCIL RECOMMENDATION of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)	I	European recommendation

COMMISSION IMPLEMENTING DECISION of 22 November 2013 on setting up the Biobanks and Biomolecular Resources Research Infrastructure Consortium (BBMRI-ERIC) as a European Research Infrastructure Consortium	I	European legislation
HUGO - Framework for responsible sharing of genomic and health-related data	I	European recommendation
European Regulation No 1901/2006 of the European parliament and of the Council on medicinal products for paediatric use 2006. The European Parliament and the Council of the European Union	I	European legislation

~~Supplement~~ Table S1

Study characteristics of the 85 included publications

Author	Year	Title	Journal	Study design	Evidence level	Nationality of first author
J. Allen, P. McCarthy, E. M. Dempsey and J. O. Hourihane	2013	Irish public would prefer legislation to protect Guthrie card archive rather than destroy it	BMJ	cross sectional study	IV	Ireland
V. Anastasova, A. Mahalatchimy, E. Rial-Sebbag, J. M. Anto Boque, T. Keil, J. Sunyer, J. Bousquet and A. Cambon-Thomsen	2013	Communication of results and disclosure of incidental findings in longitudinal paediatric research	Pediatric Allergy and Immunology	non-systematic review	III	France
Ashcroft R.E., Goodenough T., Willamson E., Kent J.	2003	Children´s consent to research participation: social context and personal experience invalidate fixed cutoff rules	The American Journal of Bioethics	expert opinion	V b	UK
J. Balaguer, A. Canete, E. Costa, S. Oltra, M. Hernandez and V. Castel	2006	Tumour banks in pediatric oncology	Clin Transl Oncol	cross sectional	IV	Spain
K. Birmingham and A. Doyle	2009	Ethics and governance of a longitudinal birth cohort	Paediatr Perinat Epidemiol	non-systematic review	III	UK
D. Budimir, O. Polasek, A. Marusic, I. Kolcic, T. Zemunik, V. Boraska, A. Jeroncic, M. Boban, H. Campbell and I. Rudan	2011	Ethical aspects of human biobanks: a systematic review	Croat Med J	systematic review	II a	Croatia
A. Cambon-Thomsen, E. Rial-Sebbag and B. M. Knoppers	2007	Trends in ethical and legal frameworks for the use of human biobanks	Eur Respir J	non-systematic review	III	France
P. Chatzipantazi, K. M. Roy, S. O. Cameron, D. Goldberg, R. Welbury and J. Bagg	2004	The feasibility and acceptability of collecting oral fluid from healthy children for anti-HCV testing	Arch Dis Child	cross sectional	IV	UK

D. Deplanque, G. Birraux, P.-H. Bertoye, E. Postaire, N. Round Table and X. Giens	2009	Collections of Human Biological Samples for Scientific Purposes. Why do Current Regulation Need to be Clarified and How?	Therapie	expert opinion	V b	France
C. M. Douglas, C. G. van El, A. Faulkner and M. C. Cornel	2012	Governing biological material at the intersection of care and research: the use of dried blood spots for biobanking	Croat Med J	expert opinion	V b	Netherlands
I. Ellis, G. Mannion and A. Warren-Jones	2003	Retained human tissues: a molecular genetics goldmine or modern grave robbing? A legal approach to obtaining and using stored human samples	Med Law	expert opinion	V b	UK
S. Eriksson, A. T. Höglund and G. Helgesson	2008	Do Ethical Guidelines Give Guidance?A Critical Examination of Eight Ethics Regulations	Cambridge Quarterly of Healthcare Ethics	cross sectional study	IV	
I. Garcia-Merino, N. de las Cuevas, J. Luis Jimenez, A. Garcia, J. Gallego, C. Gomez, D. Garcia, M. Angeles Munoz-Fernandez and H. I. V. B. Spanish	2010	Pediatric HIV BioBank: A New Role of the Spanish HIV BioBank in Pediatric HIV Research	AIDS Res Hum Retroviruses	cross-sectional study	IV	Spain
N. A. A. Giesbertz, A. L. Bredenoord and J. J. M. van Delden	2014	Clarifying assent in pediatric research	European journal of human genetics : EJHG	narrative literature review	V a	Netherlands
E. Gluckman	2000	Ethical and legal aspects of placental/cord blood banking and transplant	Haematologica	expert opinion	V b	France
B. Godard, J. Schmidtke, J.-J. Cassiman and S. Ayme	2003	Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective	European Journal of Human Genetics	non-systematic review	III	France
T. Goodenough, E. Williamson, J. Kent and R. Ashcroft	2004	Ethical protection in research: including children in the debate	Researchers and their "subjects"	cross-sectional study	IV	UK
T. Goodenough, E. Williamson, J. Kent and R. Ashcroft	2011	'What Did You Think About That?' Researching Children's Perceptions of Participation in a Longitudinal Genetic Epidemiological Study	Children and Society	non-systematic literature review	III	UK

M. G. Hansson	2009	Ethics and biobanks	British Journal of Cancer	non-systematic review	III	Sweden
M. G. Hansson	2005	Building on relationships of trust in biobank research	J Med Ethics	Expert Opinion	V b	Sweden
M. G. Hansson	2007	For the safety and benefit of current and future patients	Pathobiology	Expert Opinion	V b	Sweden
S. O. Hansson	2004	The ethics of biobanks	Cambridge Quarterly of Healthcare Ethics	Expert opinion	V b	Sweden
G. Helgesson and U. Swartling	2008	Views on data use, confidentiality and consent in a predictive screening involving children	J Med Ethics	cross sectional	IV	Sweden
G. Helgesson	2005	Children, longitudinal studies, and informed consent	Medicine, Health Care and Philosophy	narrative literature review	V a	Sweden
G. Helgesson, M. G. Hansson, J. Ludvigsson and U. Swartling	2010	What parents find important when participating in longitudinal studies: results from a questionnaire	Clinical Ethics	cross sectional study	IV	
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2009	Biological sample collections from minors for genetic research: a systematic review of guidelines and position papers	Eur J Hum Genet	systematic review	II a	Belgium
K. Hens, H. Nys, J.-J. Cassiman and K. Dierickx	2009	Genetic Research on Stored Tissue Samples From Minors: A Systematic Review of the Ethical Literature	Am J Med Genet A	systematic review	II a	Belgium
K. Hens, J. J. Cassiman, H. Nys and K. Dierickx	2011	Children, biobanks and the scope of parental consent	Eur J Hum Genet	non-systematic review	III	Belgium
K. Hens, E. Levesque and K. Dierickx	2011	Children and biobanks: a review of the ethical and legal discussion	Hum Genet	non-systematic review	III	Belgium

K. Hens, C. E. Van El, P. Borry, A. Cambon-Thomsen, M. C. Cornel, F. Forzano, A. Lucassen, C. Patch, L. Tranebjaerg, E. Vermeulen, E. Salvaterra, A. Tibben and K. Dierickx	2013	Developing a policy for paediatric biobanks: principles for good practice	Eur J Hum Genet	non-systematic review	III	Belgium
K. Hens and K. Dierickx	2010	Human tissue samples for research. A focus group study in adults and teenagers in Flanders	Genet Couns	cross-sectional study	IV	Belgium
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2011	The storage and use of biological tissue samples from minors for research: a focus group study	Public Health Genomics	cross-sectional study	IV	Belgium
K. Hens, J. Snoeck, H. Nys, J. J. Cassiman and K. Dierickx	2010	An exploratory survey of professionals on the use of stored tissue samples from minors for genetic research	Genetics and Molecular Research	cross-sectional study	IV	Belgium
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2011	Risks, Benefits, Solidarity: A Framework for the Participation of Children in Genetic Biobank Research	Journal of Pediatrics	narrative literature review	V a	Belgium
K. Hens, H. Nys, J. J. Cassiman and K. Dierickx	2011	The return of individual research findings in paediatric genetic research	J Med Ethics	narrative literature review	V a	Belgium
K. Hens, J. Wright and K. Dierickx	2009	Biobanks: oversight offers protection	Science	Letter to the editor	V b	Belgium
B. Hofmann	2009	Broadening consent-and diluting ethics?	J Med Ethics	narrative literature review	V a	Norway
S. Holm	2005	Informed Consent and the Bio-banking of Material from Children	Genomics, society and politics	expert opinion	V b	UK
C. Jackson, M. Dixon-Woods, M. Tobin, B. Young, D. Heney and K. Pritchard-Jones	2009	Seeking consent to tissue banking: a survey of health professionals in childhood cancer	Eur J Cancer Care (Engl)	cross sectional	IV	UK

V. W. V. Jaddoe, R. Bakker, C. M. van Duijn, A. J. van der Heijden, J. Lindemans, J. P. Mackenbach, H. A. Moll, E. A. P. Steegers, H. Tiemeier, A. G. Uitterlinden, F. C. Verhulst and A. Hofman	2007	The Generation R Study Biobank: a resource for epidemiological studies in children and their parents	European Journal of Epidemiology	Observational Study	III	Netherlands
S. Kirk	2007	Methodological and ethical issues in conducting qualitative research with children and young people: a literature review	Int J Nurs Stud	non-systematic review	III	UK
M. F. Laker	2006	The Human Tissue Act: implications for clinical biochemistry	Ann Clin Biochem	expert opinion	V b	UK
V. Lambert and M. Glacken	2011	Engaging with children in research: Theoretical and practical implications of negotiating informed consent/assent	Nurs Ethics	non-systematic review	III	Ireland
H. Lochmuller and P. Schneiderat	2010	Biobanking in Rare Disorders	Rare Diseases Epidemiology	expert opinion	V b	UK
N. Martin, P. Krol, S. Smith, K. Murray, C. A. Pilkington, J. E. Davidson, L. R. Wedderburn and G. Juvenile Dermatomyositis Res	2011	A national registry for juvenile dermatomyositis and other paediatric idiopathic inflammatory myopathies: 10 years' experience; the Juvenile Dermatomyositis National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies	Rheumatology	cross-sectional study	IV	UK
D. Mascalzoni, A. C. J. W. Janssens, A. Stewart, P. Pramstaller, U. Gyllensten, I. Rudan, C. M. van Duijn, J. F. Wilson, H. Campbell, R. Mc Quillan and E. Consortium	2010	Comparison of participant information and informed consent forms of five European studies in genetic isolated populations	European Journal of Human Genetics	expert opinion	V b	Italy
J. V. McHale	2011	Accountability, Governance and Biobanks: The Ethics and Governance Committee as Guardian or as Toothless Tiger?	Health Care Anal	narrative literature review	V a	UK
J. McHale, M. Habiba, M. Dixon-Woods, D. Cavers, D. Heney and K. Pritchard-Jones	2007	Consent for childhood cancer tissue banking in the UK: the effect of the Human Tissue Act 2004	Lancet Oncol	narrative literature review	V a	UK

D. F. Merlo, L. E. Knudsen, K. Matusiewicz, L. Niebroj and K. H. Vahakangas	2007	Ethics in studies on children and environmental health	J Med Ethics	narrative literature review	V a	Italy
D. F. Merlo, K. Vahakangas and L. E. Knudsen	2008	Scientific integrity: critical issues in environmental health research.	Environmental Health	narrative literature review	V a	Italy
S. E. Mumford	1999	Children of the 90s II: challenges for the ethics and law committee	Arch Dis Child Fetal Neonatal Ed	expert opinion	V b	UK
S. E. Mumford	1999	Children of the 90s: ethical guidance for a longitudinal study	Arch Dis Child Fetal Neonatal Ed	expert opinion	V b	UK
B. Norgaard-Pedersen and D. M. Hougaard	2007	Storage policies and use of the Danish Newborn Screening Biobank	J Inherit Metab Dis	expert opinion	V a	Denmark
B. Norgaard-Pedersen and H. Simonsen	1999	Biological specimen banks in neonatal screening	Acta Paediatr Suppl	expert opinion	V a	Denmark
J. Pawlikowski, J. Sak and K. Marczewski	2011	Biobank research and ethics: the problem of informed consent in Polish biobanks	Archives of Medical Science	cross-sectional study	IV	Poland
C. Petrini and M. Farisco	2011	Informed consent for cord blood donation. A theoretical and empirical study	Blood Transfus	cross-sectional study	IV	Italy
C. Petrini, L. Lombardini, S. Pupella, A. N. Costa and G. Grazzini	2011	Collection, Storage, and Allogeneic Use of Cord Blood: Informed Consent Form Used by the Italian Biobank Network	Biopreservation and biobanking	expert opinion	IV	Italy
C. Petrini, A. Olivieri, C. Corbetta, R. Cerone, G. D'Agnolo and A. Bompiani	2012	Common criteria among States for storage and use of dried blood spot specimens after newborn screening	Ann Ist Super Sanita	expert opinion	V a	Italy
C. Petrini	2012	Ethical and legal considerations regarding the ownership and commercial use of human biological materials and their derivatives	Journal of Blood Medicine	narrative literature review	V a	Italy

W. Pinxten and K. Dierickx	2008	The Implementation of Directive 2001/20/EC into Belgian Law and the Specific Provisions on Pediatric Research	European Journal of Health Law 15 (2008) 153-161	expert opinion	V b	Belgium
W. Pinxten, K. Dierickx and H. Nys	2009	Ethical principles and legal requirement for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials	Eur J Pediatr	expert opinion	V b	Belgium
O. Polasek	2013	Future of biobanks - bigger, longer, and more dimensional	Croat Med J	narrative literature review	V a	Croatia
M. M. Reid	1994	Research on leukaemia cells surplus to diagnostic needs in children	J Med Ethics	expert opinion	V b	UK
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Organization of Economic Co-operation and Development (OECD) 2009 Recommendation on Human Bioanks and Genetic Research Databases	I	International guideline regarding biomedical research and biobanks

Council for International Organizations of Medical Science (CIOMS) 2008 International Ethical Guidelines on Epidemiological Studies	I	International guideline regarding biomedical research and biobanks
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Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin (Adopted by the Committee of Ministers on 11 May 2016 at the 1256th meeting of the Ministers' Deputies)	I	European recommendation
Data storage and DNA banking for biomedical research: technical, social and ethical issues Recommendations of the European Society of Human Genetics European Journal of Human Genetics (2003) 11, Suppl 2, S8 –S10. doi:10.1038/sj.ejhg.5201115	I	European recommendation
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